# CHARACTERIZING CURRENT REGISTRATION OF PHASE 3 CROSSOVER TRIALS ON CLINICALTRIALS.GOV

by

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## ABSTRACT

Background: ClinicalTrials.gov is the primary registry for federally and privately funded clinical trials conducted in the United States. Unlike the more commonly used parallel design, in which each participant is randomized to a certain treatment, in a crossover design, each participant is randomized to a sequence of treatments and each participant serves as his/her own control in estimating treatment effect. This distinct feature makes the design and registration of crossover trials different from that of parallel trials.

Objective: To characterize Phase 3 crossover trials registered on ClinicalTrials.gov; to identify registration issues using current system; to inform the development of practical guidance to improve registration of crossover trials on ClinicalTrials.gov.

Method: We searched ClinicalTrials.gov on Sep 15, 2014 for trials labeled 'Crossover Assignment' in the intervention model, randomized, phase 3, and having results registered and citation provided. Two reviewers independently assessed the eligibility and extracted data on study design details, reporting groups, primary outcomes and adverse events to an electronic form developed on Systematic Review Data Repository. We tabulated the numbers of trials with specified characteristics and described issues in the definitions, instructions, and in using the registration template.

Results: Registration of crossover trials was mixed. Only three quarters of included Phase 3 studies (75%, 54/72) labeled as ''Crossover Assignment' trials were real randomized, crossover trials. We found variations of registration format for different sections. Majority of

the trials (81.5%, 44/54) presented the outcome following a parallel instead of crossover structure. We proposed guidance for table creation with examples for registering arms/interventions, participant flow, baseline characteristics, outcome and adverse events respectively, to help improve the registration of crossover trials on ClinicalTrials.gov.

Conclusion: Many of studies labeled as 'Phase 3 Crossover Assignment' have problems in registration on ClinicalTrials.gov The proposed strategy has the potential to improve registration of the design, results and analysis of crossover trials on ClinicalTrials.gov.

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# Chapter 1: Background

## 1.1 ClinicalTrials.gov

ClinicalTrials.gov is a publicly available and web-based clinical trials registry, maintained by the National Library of Medicine of the National Institutes of Health (NIH). It has become the primary registry for federally and privately funded clinical trials conducted in the United States. Registration at ClinicalTrials.gov began in 2000. Since 2007, the US Food and Drug Administration Amendments Act required trials that are subject to FDA regulation or funded by NIH to report basic results in the ClinicalTrials.gov database, including data elements related to participants demographics, baseline characteristics, outcomes and statistical analyses, as well as adverse events. [1]

## 1.2 Crossover design

Trials registered on ClinicalTrials.gov can utilize different designs. Unlike the more commonly used parallel randomized controlled trial where each participant is randomized to receive one of the treatments (for example, treatment A or treatment B), in a crossover trial, participants are assigned to a sequence of treatments (treatment A then treatment B or vice versa) and treatment effect is estimated based on within-individual difference as each subject serves as his/her own control [2] (Figure 1). The major advantage of using a crossover design is that, by removing the between-subject variations, in most cases, a sample size is needed to detect individual treatment differences compared to a parallel design. [3]

However, using repeated measurements of same subjects from multiple intervention periods brings in potential disadvantages, which needs special attention in design and analysis. The

first problem is the missing data issue, especially resulting from dropouts.[3] Although missing data due to dropout may challenge the analysis and interpretation for both parallel and crossover design trials, it is more of a concern for crossover trial compared to parallel one. If one subject dropped out after the first intervention in a parallel trial, data collected up to discontinuation may still contribute to analysis of treatment effect up to the time point of discontinuation; yet, in a crossover tria l, data collected from the first period would be wasted if there were missing data from the subsequent periods because a within-individual comparison is not possible. Therefore, participant flow including missing data, and time frame for measured values are of vital importance for registering crossover trials.

The second issue is the risk of carryover effect, that is, there may be a persistent or residual effect from treatment in one period on the subsequent period of treatment, such that the comparative treatment effects may be confounded. For example, if the effect of treatment A from period 1 persists to period 2, when a subject is receiving treatment B, the simultaneous treatment effects from both A and B will be observed in the second period; yet, only B's effect is considered, leading to invalid interpretation of comparative treatment effects. Another issue is the period effect, where differential secular changes may exist such that the treatment effects are not consistent over time, resulting in treatment by period interaction.

Because of these important distinctions between parallel and crossover designs, and issues specific to crossover design, the registration of the design, analysis, and results of crossover trials is different from that of parallel trials.[2] These design and analysis features need to be captured in the ClinicalTrials.gov registration format.

A recent study by Li et al. (2014) [4] evaluated the characteristics of a large number of crossover trials in glaucoma literature. They found that the design and reporting were largely inadequate and analysis inappropriate, hence limiting their value to clinicians and patients. Nearly three quarters of glaucoma crossover trials were found to present outcome data as if the trial had a parallel design and ignored the paired-nature of data. [5] Because they only focused on published literature and because ClinicalTrials.gov database has a great potential to provide evidence for clinicians, patients and researchers, we would like to examine the registration of crossover trials on ClinicalTrials.gov and provide suggestions to improve the registration.

**1.3 Definitions from ClinicalTrials.gov registry for crossover design trials**

Registry websites generally provide 'Glossary' sections for explaining terms used, and ClinicalTrials.gov did so without exception. However, we found two versions of definitions for 'crossover' on 'Glossary of Common Site Term' (referred to as 'Glossary' document in the later paragraphs) [6] webpage and 'Protocol Data Element Definitions (DRAFT)' (referred to as 'Protocol' document in the later paragraphs) [7] page, the latter one was prepared especially for study record managers for guiding registration of trial information on ClinicalTrials.gov.

The 'Glossary of Common Site Term' ('Glossary' document) [6] defined 'crossover design' as follows:

**Crossover design**

> "Describes a clinical trial in which groups of participants receive two or more interventions in a particular order. For example, a two-by-two crossover design involves two groups of participants. One group receives drug A during the initial phase of the trial, followed by drug B during a later phase. The other group receives drug B during the initial phase, followed by drug A during a later phase. So during the study, participants "cross over" to the other drug. All participants receive drug A and drug B at some point during the study, but in a different order, depending on the group to which they are assigned. One type of Intervention Model (Design)."

In the ClinicalTrials.gov Protocol Data Element Definitions (DRAFT) ('Protocol' document) [7], the term 'Cross-over' assignment was defined in the 'Intervention Model' section as: "**Cross-over**: participants receive one of two alternative interventions during the initial phase of the study and receive the other intervention during the second phase of the study".

The definition for 'cross-over' in the 'Protocol' document, although clear to some, may lead to a misunderstanding of what could be categorized as a randomized crossover trial and subsequently create registration errors on ClinicalTrials.gov. For example, some trials that have an observational phase in which all participants on the placebo arm receive the active intervention after the randomized phase would appear to meet the definition of 'cross-over' provided in the 'Protocol data elements definitions' document.

ClinicalTrials.gov also provided a registration example for a crossover design study with a two-way AB|BA crossover design from a fictional manuscript [8] and results documents [9], to

give registrars a template for registering crossover studies on ClinicalTrials.gov. Even with the definitions in 'Glossary' [6], 'Protocol' [7] data elements documents and the sample example [8, 9] for presenting crossover features, it is still not clear how to register appropriately using the table-format reporting structure on ClinicalTrials.gov.

### 1.4 Exploration of other registries

An exploratory search of 15 primary clinical trials registries listed on the WHO International Clinical Trials Registry Platform [10] in December 2014, showed that only a few registries provided definitions or glossary entries for a crossover design.

Australia and New Zealand Clinical Trials Registry (ANZCTR) defined crossover assignment in the data field explanation document as: 'Crossover: All participants receive all the interventions in different sequences during the study. They act as their own control.'[11]

The EU Clinical Trials Register (EU-CTR) glossary had a definition for the term 'Cross over' as 'Comparison of two (or more) treatments in which patients switched to the alternative treatment after a specified period of time'. [12]

The German Clinical Trials Register (DRKS) defined 'Crossover Assignment' as 'There are several groups (at least two), which receive every or at least several treatments in different sequences'. [13]

In summary, no uniform definition exists among these network registries. Discrepant definitions can confuse registrants and hinder the proper registration of crossover trials.

# Chapter 2: Methods

## 2.1 Specific aims

Aim 1: To review and characterize the registration of design, analysis and results of phase 3 crossover trials on ClinicalTrials.gov;

Aim 2: To identify issues in registration using current format;

Aim 3: To inform the development of practical guidance to improve registration of crossover trials on ClinicalTrials.gov.

## 2.2 Selection of studies

Studies registered on Clinicaltrials.gov meeting the following criteria will be eligible for inclusion.

Eligibility criteria:

- Trials labeled as 'Crossover Assignment' in the intervention model
- Randomized trials
- Phase 3 (study phase) trials
- Trials with results registered by the search date (September 15, 2014)
- Trials with citations/publications linked to ClinicalTrials.gov
- Trials with at least one primary outcome registered on ClinicalTrials.gov by the search date (September 15, 2014).

## 2.3 Search strategy

A colleague from ClinicalTrials.gov searched ClinicalTrials.gov on September 15, 2014, using the registry's 'Advanced Search' function with the following key terms: 'Crossover

Assignment' (in 'Intervention Model'), any text (not blank) in the 'Results First Received Date' and 'Citation' section and sent us 367 studies (see Appendix 1 for search strategy). For the search results, we selected studies labeled as 'Phase 3' and 'Allocation' as 'Randomized' for this project. Two individuals working independently manually evaluated each registration identified from the search against the eligibility criteria. In the case when the ClinicalTrials.gov registry provides insufficient information to determine if the trial was a randomized crossover trial, we referred to citations provided by trial sponsors or investigators, indexed in the 'Publications' section on ClinicalTrials.gov. If more than one publication were listed, we manually checked all publications. If no indexed publication provided the information we need, we manually searched PubMed using the trial's NCT number or the conditions, interventions, investigators information registered on ClinicalTrials.gov. We resolved data abstraction discrepancies through adjudication or consultation with a third person on the team.

Data extraction

For those registrations that met our eligibility criteria, using the 'Download' search results function, we exported the following data elements from data fields available from ClinicalTrials.gov:

- Study identification, including 'Organization's Unique Protocol ID', 'Official Title' and 'Study Type';
- Study status, including 'Overall Recruitment Status', 'Primary Completion Date';
- 'Sponsor' and 'Responsible Party' (investigator's information);

- Oversight information, including ‘FDA Regulated Intervention?’ (Indicator of whether the trial includes an intervention subject to FDA regulation);
- Study description, including ‘Brief Summary’ and ‘Detailed Description’; ‘Conditions’;
- Study design, including ‘Primary Purpose’, ‘Study Phase’, ‘Intervention Model’, ‘Number of Arms’,’ Masking’, ‘Allocation’, ‘Study Classification’, and ‘Enrollment’;
- Arms information, including ‘Arm Label’, ‘Arm Type’ and ‘Arm Description’
- ‘Participant Flow’ section, including ‘Recruitment Details’, ’Pre-assignment Details’, ‘Arm Title’, ‘Arm Description’ and ‘Period Title’;
- ‘Baseline Characteristics’ section, including ‘Arm Title’, ‘Arm Description’, ‘Overall Number of Baseline Participants’, ‘Baseline Analysis Population Description’, ‘Baseline Measure Title’, ‘Measure Type’, ‘Measure Dispersion’, ‘Category Title’ and ‘Baseline Measure Data’;
- Outcome Measures section, including ‘Outcome Measure Type’, ‘Outcome Measure Title’, ‘Outcome Measure Description’, ‘Outcome Measure Time Frame’, ‘Outcome Measure Safety Issue’, ‘Arm Title’, ‘Arm Description’, ‘Number of Participants Analyzed’, ‘Type of Units Analyzed’, ‘Analysis Population Description’, ‘Measure Type’, ‘Measure of Dispersion/Precision’, ‘Category Title’, ‘Statistical Analysis Overview’, ‘Statistical Test’, ‘Method of Estimation’ and ‘Estimation Comments’;
- ‘Serious Adverse Events’ and ‘Other Adverse Events’ section, including ‘Arm Title’ and ‘Arm Description’;
- Links information, ‘URL’ and ‘Description’.

In addition to the data fields that we exported directly from ClinicalTrials.gov, two individuals independently extracted the following information from a manual review of the registration:

1) ‘Arms’ and ‘Assigned Interventions’

   ‘Arms’ section on ‘Full Text View’ page provides the name for identifying the arms, and brief description for each arm to distinguish it from other arms in the trial. ‘Assigned Interventions’ specifies the interventions used for that arm, next to the ‘Arms’ information in a table format. A key feature differentiating crossover trial from parallel one is that, participants are randomized to a sequence of interventions, instead of certain intervention(s), and thus, the specified arms in a crossover trial should represent the randomized sequences in each trial (registered ‘By sequence’), instead of one intervention for one arm in a parallel trial (usually registered ‘By intervention’). It is important to identify how registrars presented arms and interventions for crossover trials. We abstracted the method of registration of the trial arms and study interventions in the current table format in the registration system, and summarized the variation of registration: ‘By sequence’, ‘By intervention’, ‘By period’ or ‘Others’ (see example 15 in Appendix 3). We proposed an appropriate and consistent approach for registering ‘Arms’ and ‘Assigned Interventions’.

2) Classification of study design

   By reviewing the trial description, arms description and treatment assignments, we then identified the number of compared interventions used in the trial, the number of treatment

periods and the number of sequences registered, and summarized the study design. For example, a simple crossover design comparing two treatments, with two periods and therefore two sequences was expressed as 'AB|BA' design. We summarized the different crossover designs of all included trials.

3) 'Reporting Groups'

Reporting Groups' is used by the ClinicalTrials.gov template to create the column names in each section. When registering results in ClinicalTrials.gov, trial sponsors or investigators would specify the Reporting Groups for 'Participant Flow', 'Baseline Characteristics', 'Outcome measures' and 'Adverse Events' sections respectively. For example, if a registration specified that the 'Reporting Groups' in 'Participant Flow' section is by sequence (see example 22 in Appendix 3), the column names for 'Participant Flow' table would be labeled according to the different sequences. The similar structure applies to 'Reporting Groups' in different sections of the registration, which can be created differently from other sections. We recorded how the 'Reporting Groups' for each section were registered. We summarized the variations for registering 'Reporting Groups' and provided appropriate examples for each section.

4) 'Participant Flow'

The progress of research participants through each stage of the trial is documented in a tabular format on ClinicalTrials.gov, which may be separated into several 'periods', with each period presented by a separate table. We recorded how participant flow information was reported in the table format on ClinicalTrials.gov, including whether tables were

presented by period, intervention, etc. (see example 23 in Appendix 3), and whether the run-in or washout periods were presented or explained. We summarized the variations in table presentation and addressed the appropriateness of different ways for presenting participant flow for a crossover trial.

5) 'Outcome Measures'

Trial outcome data are also presented in a tabular format on ClinicalTrials.gov. Descriptive information is registered for outcome titles, description and time frame. Numeric data and description of statistical analyses are registered for outcomes. We included studies with results of at least one primary outcome available, and for the purpose of this study, we abstracted data from the first registered primary outcome if there is more than one primary outcome registered. We summarized the 'specific metric', 'method of aggregation', specified 'time frame' for each outcome type (continuous outcome, categorical outcome, and time-to-event outcome) following the framework proposed by Zarin, et al (2011) [14], as well as the registering of the analysis population, methods of statistical analyses and associated issues.

**2.4 Data management**

We have provided a paper version of our online form in Appendix 2. We used Systematic Review Data Repository (SRDR) for data collected and management [15]. Data were collected and coded on SRDR with unique NCT [16] identifiers linked to each trial. After data extraction and adjudication was completed, we exported extracted data from SRDR for analysis.

### 2.5 Statistical analysis

We tabulated the distribution of each characteristic of the included trials using STATA 13®. We described issues in the definitions, instructions, and in using the registration template, ordered by the sections listed in the registration system.

# Chapter 3: Results

## 3.1 Eligible studies

Using our search strategy (Appendix 1) through ClinicalTrials.gov search query on September 15, 2014, we identified a total of 367 'Crossover Assignment' studies with 'results' and 'citations' reported on ClinicalTrials.gov (Figure 2). We excluded 9 trials with allocation labeled as 'Non-randomized', 286 trials with study phases other 'Phase 3, and 18 trials that we judged as not randomized crossover trials, respectively (Figure 2). We included 54 studies in our subsequent data abstraction (Figure 2).

## 3.2 Characteristics of included phase 3 randomized crossover trials

Crossover-design trials registered on clinicaltrials.gov tested interventions for a variety of conditions, ranging from asthma, pain, and migraine to prostate cancer and chronic kidney disease (stage 5), etc. Table 1 summarizes the registration characteristics of 54 phase 3 randomized crossover trials. Trial characteristics in Table 1 are provided and listed in 'Protocol' document, except for the last item 'Crossover design sequence', which was summarized by reviewers for certain crossover design. The majority of trials (77.8%, 42/54) were registered using 'double blind'. Among those 42 trials that registered 'double blind', almost all trials (97.6%, 41/42) had 'Subject' masked, 42.9% (18/42) had 'Caregiver' masked, and 95.2% (40/42) for 'Investigator' and 42.9% (18/42) for 'Outcome Assessor' respectively.

Based on the information provided in 'Purpose' and/or trial 'Detailed Description' sections on 'Full Text View' page on ClinicalTrials.gov, we identified that nearly two thirds (64.8%,

35/54) of the included trials used a simple 'AB|BA' crossover design and 20.4% (11/54) of the trials used a balanced and complete block of six sequences design 'ABC|ACB|BCA|BAC|CAB|CBA'. The remaining 7.4% (8/54) trials used designs with repeated treatment periods, such as 'ABA|BAB' (NCT00131248) [17] and 'AAB|ABA|BAA' (NCT00812006) [18]; incomplete block designs such as 'ABC|BAC|CAB' (NCT00999908) [19], or others. Two studies used more than 6 sequences in the crossover design: 12 sequences in trial NCT00615030 [20] with a total sample size of 96 participants, and 18 sequences in trial NCT01072149 [21] with a total sample size of 54 participants.

### 3.3 Registration of 'Arms' and 'Assigned Interventions' section

In order to explore the variations in registering crossover trials, we provided examples of how arms and interventions are currently registered in Appendix 4. For 47 trials using a complete block design, where participants received all interventions in a trial through different periods, 27 trials presented the same information in the 'Assigned Interventions' cells for all rows, as all interventions were checked in the 'Cross-Reference' table for each arm in the registration system. We found a variety of registration formats for 'Assigned interventions' and 'Arms' in the included studies, with nearly one third (31.5%, 17/54) registered the 'Reporting Groups' in 'Arms' section 'by Intervention', similar to a parallel design trial, and nearly two thirds (63.0%, 34/54) registered by Sequence. The reviewers were unable to categorize the registration of 'Assigned interventions' and 'Arms' for 5.6% (3/54) of the trials.

We present below three examples of poor registration of arms/interventions. Trial NCT00894556 [22] registered three sequences in the first three rows of the 'Arms' section, and included an additional arm labeled as 'Baseline Phase' (Figure 3), which would be confusing to be included as an arm of the trial. 'Arms' section for this crossover trial should be used to specify compared sequences and information from the first three rows in the figure would be sufficient.

Trial NCT00200967 [23] recruited two genotype subpopulations in the trial with the objective to compare the treatments effects between two populations. Each genetic subpopulation was registered as one arm of the trial and two-sequence crossover within each genetic subpopulation was specified in 'Arms description' under each subpopulation (Figure 4). The presentation and explanation was not clear enough to clarify the exact comparison arms of the trial, either two subpopulations or two crossover sequences within each subpopulations.

Trial NCT00395304 [24], with a complete block three-treatment, three-periods, six sequences crossover design, registered all crossover sequences in one 'Arm' cell in the registration system (Figure 5). Every arm in this trial received the exact same interventions but in different orders. The arms/interventions table is designed for specifying one arm in one row in the registration system. We suggest that the six arms should be specified in six different cells in the registration system instead of piling in the same cell, and using the 'cross-reference' function in the system to specify the assigned interventions for each arm accordingly, resulting in six rows in the arms/interventions section, each row representing one arm only.

### 3.4 Registration of 'Participant Flow' section

Majority of included trials (92.6%, 50/54) registered 'Arms/Groups Title' by Sequence, 5.6% (3/54) by Intervention, and 1.9% (1/54) registered in a way that could not be categorized by the reviewers. Trial NCT00364182 [25] registered the 'Reporting Groups' in 'Participant Flow' section both by Sequence and by Period (Figure 6), separating the pre-randomization and post-randomization participant flow information in different reporting groups rather than presenting periods in the subsequent tables.

In terms of presenting the 'Participant Flow' tables, most of the trials (85.2%, 46/54) presented separate tables by period, but still, 14.8% (8/54) of trials provided only one table for the 'overall/total study population', which essentially failed to provide information about participant flow through several periods in the trial. Twenty-four (44.4%, 24/54) trials presented the flow through non-treatment periods in addition to treatment periods, including tables for pre-randomization and/or washout periods (Table 2). Less than half of included trials (37.0%, 20/54) clearly stated or showed that a washout period was included in the 'Purpose' and 'Detailed Description' of the Arms/Intervention section, in the 'Participant Flow' section, or in text descriptions.

We observed a few exceptions in how the 'Participant Flow' was registered. Trial NCT00894556 [26] (Figure 7) used participant flow tables to present two study periods: one pre-randomization phase (labeled as 'Baseline Phase') and one post-randomization phase (labeled as 'Treatment Phase') without showing flow within the treatment phase through

crossover periods. Trial NCT00565266 [27] (Figure 8) created one reporting group for the entire study, without separating the flow of participants assigned to different sequences through different periods.

### 3.5 Registration of 'Baseline Characteristics'

Of the 54 included trials, almost all trials (96.3%, 52/54) presented characteristics for the entire study population. Additionally, we found 38.9% (21/54) of trials presented baseline characteristics by sequence, and 5.6% (3/54) presented by period. For those including the 'Total' group, we observed variations in terms used to describe the group, such as 'Overall Study Population', 'Entire Study Population', 'All participants', 'Safety Population' (i.e.: defined as 'Participants who were randomized and who treated at least one migraine attack with investigational product in trial NCT00382993 [28]).

### 3.6 Registration of 'Outcome Measures'

The number of primary outcomes registered ranged from one to eight. Majority of trials (88.89%, 48/54) registered one primary outcome. Trial NCT00837967 [29] and trial NCT00666263 [30] registered 6 and 8 primary outcomes respectively.

In terms of outcome type, 74.1% (40/54), 9.3% (5/54), 3.7% (2/54) registered the first primary outcome as continuous, categorical and time-to-event outcomes respectively. In 13.0% (7/54) of the registered trials, we could not categorize the outcome type based on the provided information. Table 3 shows the summary statistics for specific metric and method of aggregation for the 1st primary outcome. Explanation for the 'Time Frame' information

was mixed. We found more than one third (38.9%, 21/54) of trials did not clearly explain the 'Time Frame' for the outcome, only defining the time frame for the measurement duration (i.e.: outcome was measured after 2-4 hours of administration), without providing sufficient information on whether data are collected during all periods or a subset of periods (i.e.: unclear about whether outcome was measured after 2-4 hours of administration from period 1 and period 2, or from 1st period only).

For 'Reporting Groups' in the primary outcomes section (description of primary outcomes), most of trials (81.5%, 44/54) registered by Intervention, similar to that in the parallel trials, and only a few (9.3%, 5/54) registered by Sequence. One trial (1.8%, 1/54) presented the by Total only, 1 (1.8%, 1/54) trials by Period, and 5.6% (3.54) in other ways (i.e., grouped by subpopulation in trial NCT00200967 [29]; one group only instead of presenting compared arms, (i.e.: titled as 'Ciclesonide Versus Mometasone' in trial NCT01401465 [31] and titled as 'Tapentadol' in trial NCT00594516 [32], Figure 9).

Description of 'Analysis Population' plays an important role in understanding how outcome data is collected and analysis in a certain trial. Yet, we found 16.6% (7/54) of trials were missing in describing 'Analysis Population' for primary outcome. Of those 83.4% explaining the analysis population in the 'Population Description' field, 'Intention-To-Treat (ITT)' (29.6%, 16/54), 'Per-Protocol (PP)' (13.0%, 7/54), 'modified Intention-To-Treat (mITT)' (13.0%, 7/54) and 'Full Analysis Set (FAS)' (13.0%, 7/54) were frequently used by registrars and explained in their own ways for different trials. The remaining 14.8% (8/54) defined the analysis population using free text in the way without using above frequent terms, and

reviewers were unable to categorize as one of the term above. Similar to previous reports showing variations in defining analysis population in trials in published literature [33, 34], reviewers in this project observed many variations in the descriptions used by registrants for each type of analysis population, especially when free text was used for input. Some examples of the descriptions for ITT were shown below, and the variations in descriptions for FAS, PP and mITT were much greater.

- *"ITT. Although only 157 participants completed all three treatment periods, there was sufficient data on 8 additional participants to include them in the analysis of the primary outcome."* (Trial NCT00395304 [35])
- *"Intention-to-treat (ITT) population: all enrolled participants"* (Trial 00364182 [36])
- *"ITT (Intent-to-Treat) Population - included subjects in the Safety Population who provided an evaluation of their study drug for at least one treated attack."* (Trial 00382993 [28])

In assessing how period-specific values were presented in the table format on ClinicalTrials.gov, we found only 5.5% (3/54) of trials specified measured values with correspondent periods, and 94.4% (51/54) of trials failed to provide period specific measured value and presented one measure value only for each reporting group. Although all studies had at least one measured values of the primary outcome(s) registered, less than sixty percent (59.3%, 32/54) of the trials provide descriptions of the statistical analysis on ClinicalTrials.gov and more than forty percent failed to provide statistical analysis information.

### 3.7 Registration of 'Adverse Events'

All the included trials had 'Serious Adverse Events' and/or 'Other Adverse Events' (Table 2) registered, and majority of them (87.0%, 47/54) registered by Intervention as were in parallel trials. Only 7.4% (4/54) of trials registered by Sequence and 7.4% (4/54) teased out the counts of adverse events by Period. We found three trials (NCT00364182 [36], NCT00518531 [37], and NCT00904670 [38]) registered both by intervention and by period, and one trial (NCT00494143 [39]) registered both by sequence and by intervention. We were unable to categorize the reporting groups registered for one trial (NCT01808755 [40]).

# Chapter 4: Discussion

To our knowledge, this study is the first study to characterize and evaluate registration and reporting of randomized, crossover-design trials on ClinicalTrials.gov. We selected Phase 3 trials only for this review, since they are more likely to have results published in full in the scientific literature [41]. The methods used in this study can be applied to evaluate crossover trials from all other phases and the problems identified with registration are likely similar for early phase trials.

The ideal strategy for improving registration is to suggest minimal changes that can be adapted to the current structure on ClinicalTrials.gov registry. Our review focused on evaluating whether the registration of the design, analysis, and results of randomized crossover trials in clinicaltrials.gov under the current format in the registry system properly captures the crossover design features. We then provided recommendations for registering 'Arms/Assigned Interventions', 'Participant Flow', 'Baseline Characteristics', and two for continuous and binary primary outcomes for 'Outcome Measures' respectively.

## 4.1 Registration issues and implications

### 4.1.1 Misclassification of 'Crossover Assignment' as 'Intervention Model'

Our review showed that 25% of phase 3 trials labeled as 'Crossover Assignment' in the intervention model on ClinicalTrials.gov were not using a crossover design for allocating experimental interventions; instead, these trials were typically allowing intervention changes during the course of the trial which were not randomized. The differences in clarifying

'crossover' as an experimental design versus crossovers during observation, either per protocol or as protocol violation, need to be addressed. It has to be made clear to registrars that those allowing participants to 'crossover' to other interventions should not be categorized as 'Crossover Assignment'. The term 'crossover' should be used as the specified intervention model if the goal is to compare treatment differences using within-subject measurements on different interventions.

The definitions for 'crossover' provided in 'ClinicalTrials.gov Protocol Data Element Definitions' document [8] should be edited to clarify the use of the crossover as an experimental design feature to avoid further misclassifications of trials. The definition for 'Crossover Design' in the 'Glossary'[7] on ClincialTrials.gov correctly states that the sequences for comparison of the arms should be randomized; yet, the objective of analysis and how data should be aggregated are missing from the definition. The feature of having participants receiving multiple sequences of treatments is not sufficient to make a trial a 'crossover' trial. [3] The CONSORT statement has not been extended to cover the crossover design yet [45], and there are no guidelines available for appropriate registration and reporting of crossover design trials in publications or registries. A consistent definition for 'Crossover Design' is needed, so that further reporting instructions can be developed.

### 4.1.2 Proposing a good way for registering in the table format on ClinicalTrials.gov

We observed many variations among the naming of Arms/Interventions and 'Reporting Groups' for each section (examples shown and annotated in **Chapter 3. Results**).

- *Recommendation 1: Registering 'Arms/Interventions' section*

  In a typical two-arm parallel design trial with two experimental interventions A & B, each registered arm corresponds to one intervention. The presentation of the Arms/Interventions table is straightforward and illustrated in Figure 10 (upper panel). An example of registering a AB|BA crossover design trial was presented in Figure 10 (lower panel). The arm in a crossover trial essentially refers to one sequence, and thus, registrars would choose all related interventions used in this particular sequence by checking interventions in the 'cross-reference' section in the ClinicalTrials.gov registration system. If the crossover design were balanced and complete, the assigned interventions cells would be exactly the same across all rows in the 'Assigned Interventions' column shown on 'Full Text View' page.

For 'Participant Flow', 'Baseline Characteristics', 'Outcome Measures' and 'Adverse Event', registrars would need to specify the reporting groups separately for each section. The specified 'Reporting Groups' are then used to create the column groups for registering comparisons groups in each section.

- *Recommendation 2: Registering 'Participant Flow'*

  In the 'Participant Flow' section, a reasonable way to report groups is by sequence and to present separate tables for randomized intervention periods. Other pre-randomized periods, open-label phases, run-in, run-out, and washout periods etc. can also be presented by adding more period-tables in addition to the intervention periods in the

participant flow section to illustrate flow. A proposed way of registering the 'Participant Flow' section is shown in Figure 11.

- *Recommendation 3: Registering 'Baseline Characteristics'*

  For 'Baseline Characteristics', the comparison of interest is in the baseline characteristics by different assigned sequences. Therefore, registrars could report characteristics by sequence (Figure 12) in this section, in addition to registering a 'Total' column.

- *Recommendation 4: Registering 'Outcome Measures' for continuous and binary* outcomes

  For 'Outcome Measures', the way reporting groups are created has to do with the trial objectives, the outcome types, and potentially the ways data were analyzed. We found it difficult to determine the outcome type, specific metric, time frame and method of aggregation from 'Outcome Measures' due to inadequate description of trial details on ClinicalTrials.gov. Built upon a previous study[4] with an example of registering continuous outcome for an AB|BA crossover trial, we propose a transformed table for registering continuous outcomes to fit into the current table format on ClinicalTrials.gov registration system (Figure 13). Figure 14 illustrates a registration format of binary outcome for an AB|BA crossover-design trial, where numbers from each period and each sequence, as well as the concordant and discordant counts are listed in the measured values table accordingly.

As participants in a crossover trial receive at least two or more interventions, the ideal presentation for adverse events is to present the analysis of adverse events by intervention and by periods. However, how the event counts are to present mainly depends on the rationale of study design, teasing out events resulting from different interventions, and the availability of collected data, by periods separately.

- *Recommendation 5:* Registering statistical analyses

  More than 40% of trials were missing in the statistical analyses for the 1st primary outcome, and much fewer presented period-specific measured values. With inadequate information on measured values and statistical analyses, the summary data provided on ClinicalTrials.gov is of limited use to readers since it is difficult to interpret the meaning of the results. Currently, for non-inferiority or equivalence trials, it is 'Conditionally required by ClinicalTrials.gov' to identify whether the statistical analysis was testing non-inferiority or equivalence by checking in the registration system, and to include a definition of the non-inferiority margin and other key design parameters [8]. We suggest that the paired-nature of data in the crossover design trial needs to be addressed when registering trial results on ClinicalTrials.gov. A similar checking question to non-inferiority or equivalence trial could be used to identify crossover trial as well

### 4.1.3 Registration of time-to-event data

When it comes to time-to-event data, appropriate registration of outcome data becomes more challenging, especially for fitting in the table template provided by ClinicalTrials.gov. Among included studies, we found two trials registering the primary outcome as a time-to-

event outcome, trial NCT00004635 [42] (Figure 15) and trial NCT01808755 [43]. These two trials presented one median or mean of the primary outcome in 'Outcome Measure' section; yet, neither of the trials provided statistical analysis for the primary outcome. A potential strategy is to report the repeated measurement events at several time points (for example, the n(%) with event at time *t*, at time *t+1*, at time *t+2*, etc.), an idea used in trial NCT00500149 [44], where registrars reported measured values at several time points (Figure 16). Further evaluation is needed to propose a proper way for registering time-to-event data on ClinicalTrials.gov.

### 4.2 Proper use and registration of crossover designs

Using a crossover design has several merits. The most important one is to remove factors attributable to between-subject differences that may affect intervention comparisons. By comparing treatment effects within each participant, a crossover trial could be more efficient (i.e., require a smaller sample size) than a parallel-design given the same assumptions for sample size [45]. However, the potential disadvantages of using a crossover design include the potential carryover effect and period effect. Very few trials included in this project described clearly the rationale for using a crossover design or addressed the potential carryover effect.

Losses to follow-up can be particularly serious for crossover designs. Each participant in a crossover-design trial contributes data for two or more periods, and data from multiple intervention periods is collected and aggregated to estimate the overall effect so all periods are potentially unusable when a participants is lost to follow-up. It is important to show the

participant flow through each intervention period, as well the run-in, washout periods if applicable.

### 4.3 Limitations

There are several limitations with this study. First of all, we chose a sample of trials by examining phase 3 trials only as our first step for approaching registration issues related to crossover design trials on ClinicalTrials.gov registry. We expect that phase 1 and 2 trials have similar registration problems but cannot ensure that these results generalize to other phases.

In evaluating 'Outcome Measures', we focused on the first listed primary outcome when more than one primary outcome was registered and reported. The majority (88.9%) of trials listed only one primary outcome but it is possible that the other primary outcomes that we did not review had different registration problems.

Since there are currently no CONSORT guidelines on how crossover designs should be reported, [46] we did not compare the results posted on ClinicalTrials.gov to the results in the primary publication.

A next step is to compare the information reported on ClinicalTrials.gov with publications for each trial to figure out the registration and reporting discrepancies, quality and identify the limitations and strengths of using current registration format on ClinicalTrials.gov.

### 4.4 Strengths

It is important for ClinicalTrials.gov to understand the key issues related to crossover design trial and provide appropriate guidance for registrars to correctly register trial details on the registry. This research project is funded by a contract from ClinicalTrials.gov. By providing recommendations tailed to crossover trials and requiring minimal changes to the current database structure, the results from this project would be taken up by ClinicalTrials.gov soon.

To our knowledge, the CONSORT group is currently working on gathering data on crossover trials to develop reporting guidelines for crossover trials. This research project comes out timely to provide some insights for them to take in. From this research, we realized the inadequate understanding of crossover design trial among trialists, resulting in misclassifying the intervention model and missing in presenting key features specific to crossover design on the trial registry. In the end, it's the trialists' responsibility to understand the design, use it properly, and register the trial with sufficient details to ensure the readers of its validity and credibility.

## Chapter 5: Conclusion

In conclusion, many of trials registered on ClinicalTrials.gov, labeled as “Phase 3 Crossover Assignment”, have problems in registering the design, results and analysis of crossover design trials on the trial registry. Clear understanding of crossover trial and associated analytic and reporting issues, as well as good understanding for registration database structure plays the key roles for providing valid data on the trial registry. The addressed issues and proposed strategies have the potential to improve registration of the design and results of crossover trials on ClinicalTrials.gov, and provide insights for other groups to provide guidance on better registration of crossover trials.

**Table 1. Characteristics of phase 3 crossover trials registered on ClinicalTrials.gov searched by Sep.15 2014 (n = 54)**

| Item | Characteristics ‾ | Number | (Percent) |
|---|---|---|---|
| Study classification | Efficacy Study | 17 | (31.5%) |
| | Safety/Efficacy Study | 32 | (59.3%) |
| | Safety | 1 | (1.9%) |
| | Pharmacodynamics | 1 | (1.9%) |
| | (Blank) | 3 | (5.6%) |
| Funding source | Industry | 43 | (79.6%) |
| | Other \| Industry | 1 | (1.9%) |
| | Other | 3 | (5.6%) |
| | Other \| NIH | 4 | (7.4%) |
| | Other \| U.S. Fed | 2 | (4.0%) |
| | NIH \| Other \| U.S. Fed | 1 | (1.9%) |
| Intervention type | Drug | 47 | (87.0%) |
| | Biological | 3 | (5.6%) |
| | Device | 3 | (5.6%) |
| | Dietary Supplement \| Drug | 1 | (1.9%) |
| Masking | Open Label | 9 | (16.7%) |
| | Single Blind | 3 | (5.6%) |
| | Double Blind | 42 | (77.8%) |
| Masking parties for double blind trials | Subject | 41 | |
| | Caregiver | 18 | |
| | Investigator | 40 | |
| | Outcome Assessor | 18 | |
| | N/A | 12 | |
| Crossover sequence design | AB\|BA | 35 | (64.8%) |
| | ABC\|ACB\|BCA\|BAC\|CAB\|CBA | 11 | (20.4%) |
| | AAB\|ABA\|BAA | 2 | (3.7%) |
| | ABC\|BAC\|CAB | 1 | (1.9%) |
| | ABA\|BAB | 1 | (1.9%) |
| | Others | 4 | (7.4%) |

‾: The above trial characteristics, except for those listed in 'Crossover sequence design' section, are provided and listed on ClinicalTrials.gov in the 'Protocol'[8] and/or 'Basic results' [47] documents for guiding registration.

**Table 2. Summary of Crossover Design features for 'Arms', 'Assigned Interventions', 'Participant Flow', 'Baseline Characteristics' and 'Adverse Events' Sections**

| Characteristics | Number | (Percent) |
|---|---|---|
| **'Arms' section** | | |
| By Sequence | 34 | (63.0%) |
| By Intervention | 17 | (31.5%) |
| By Period | 0 | (0%) |
| Cannot tell | 3 | (5.6%) |
| **'Assigned Interventions' section** | | |
| Same treatment details for all rows | 26 | (48.1%) |
| Treatment details not the same for all rows | 27 | (50.0%) |
| Others | 1 | (1.9%) |
| **'Reporting Groups' in 'Participant Flow' section** | | |
| By Sequence | 50 | (92.6%) |
| By Intervention | 3 | (5.6%) |
| By Period | 1 | (1.9%) |
| Others | 1 | (1.9%) [§] |
| **Presentation of 'Participant Flow' Tables** | | |
| One table only for overall study/ total population | 8 | (14.8%) |
| Separate tables by Period, without pre-randomization and/or washout periods | 22 | (40.7%) |
| Separate tables by Period, with pre-randomization and/or washout periods | 24 | (44.4%) |
| Others | 0 | (0.0%) |
| **'Reporting Groups' in 'Baseline Characteristics' section** | | |
| By Sequence | 21 | (38.9%) |
| By Intervention | 0 | (0.0%) |
| By Period | 3 | (5.6%) |
| By Total | 52 | (96.3%) |
| Others | 6 | (1.1%) |
| **'Reporting Groups' for 'Adverse Events'** | | |
| By Total | 2 | (3.7%) |
| By Sequence | 4 | (7.4%) |
| By Intervention | 47 | (87.0%) |
| By Period | 4 | (7.4%) |
| Others | 1 | (1.8%) |

[§]: One trial (NCT00200967)[23] labeled the 'Reporting Groups' in 'Participant Flow' section 'by Population' with the goal of comparing treatment effects from two populations with different genotypes.

**Table 3. Summary of 'Outcome Measures' section**

| Characteristics | Number | (Percent) |
|---|---|---|
| **Number of primary outcome registered** | | |
| 1 | 48 | (88.89%) |
| 2 | 2 | (3.7%) |
| 3 | 2 | (3.7%) |
| > 3 | 2 | (3.7%) |
| **Types of the 1st primary outcome ∓** | | |
| Continuous outcome | 40 | (74.1%) |
| Categorical outcome | 5 | (9.3%) |
| Time-to-event outcome | 2§ | (3.7%) |
| Cannot tell | 7 | (13.0%) |
| **Specific metric for the 1st primary outcome** | | |
| Value at a time-point | 32 | (59.3%) |
| Time-to-event | 2 | (3.7%) |
| Change from the baseline before randomization | 1 | (1.9%) |
| Change from the period-baseline | 6 | (11.1%) |
| Within-individual difference between values at the end of each period | 3 | (5.6%) |
| Within-individual difference between changes from baseline | 1 | (1.9%) |
| Others | 3 | (5.6%) |
| Cannot tell | 6 | (11.1%) |
| **Method of aggregation for the 1st primary outcome ∓** | | |
| Number | 11 | (20.4%) |
| Mean | 19 | (35.2%) |
| Median | 3 | (5.6%) |
| Least squares mean | 19 | (35.2%) |
| Proportion / percent | 2 | (3.7%) |
| **'Time Frame' for 1st primary outcome includes all randomized periods** | | |
| Yes | 33 | (61.1%) |
| Cannot tell | 21 | (38.9%) |
| **'Analysis Population' for the 1st primary outcome** | | |
| ITT (intention-to-treat) | 16 | (29.6%) |
| PP (per-protocol) | 7 | (13.0%) |
| mITT (modified intention-to-treat) | 7 | (13.0%) |
| FAS (full analysis set) | 7 | (13.0%) |
| Not reported | 9 | (16.6%) |
| Others | 8 | (14.8%) |

**Table 3. Summary of 'Outcome Measures' section (continued)**

| | | |
|---|---|---|
| **'Reporting Groups' for primary outcome(s)** | | |
| By Sequence | 5 | (9.3%) |
| By Intervention | 44 | (81.5%) |
| By Period | 1 | (1.8%) |
| By Total | 1 | (1.8%) |
| Others | 3 | (5.6%) |
| **'Measured Values' presented by Period** | | |
| Yes | 3 | (5.5%) |
| No | 51 | (94.4%) |
| **Provides 'Statistical Analysis' for the 1st primary outcome** | | |
| Yes | 32 | (59.3%) |
| No | 22 | (40.7%) |
| **Statistical methods for analyzing 1st primary outcome** [Ŧ] | ( n = 32) | |
| ANCOVA | 3 | (9.4%) |
| ANOVA | 11 | (34.4%) |
| Cochran-Mantel-Haenszel | 1 | (3.1%) |
| Generalized Estimating Equations | 2 | (6.2%) |
| Generalized Linear Mixed Model | 2 | (6.2%) |
| Linear mixed effects model | 1 | (3.1%) |
| Mixed Models Analysis | 3 | (9.4%) |
| Mixed effects ANOVA crossover model | 1 | (3.1%) |
| Non-Inferiority/Equivalence Test | 2 | (6.2%) |
| Prescotts Test | 1 | (3.1%) |
| t-test | 1 | (3.1%) |
| Two-sided Signed Rank Test | 1 | (3.1%) |
| Wilcoxon (Mann-Whitney) | 2[¶] | (3.1%) |
| Wilcoxon signed rank | 1 | (3.1%) |

[Ŧ]: The characteristics options in this item are provided in 'Protocol' and/or 'Basic Results' documents by ClinicalTrials.gov for guiding registration. Otherwise, other characteristics are summarized by reviewers.

[¶]: Trial NCT01132118 reported two different statistical analysis method: 'Wilcoxon (Mann-Whitney)' and 'Regression, Linear' for the first primary outcome.[48]

[§]: Time-to-event outcome reported as Continuous Data

**Figure 1. Illustration of the design and analysis of a crossover trial [5]**

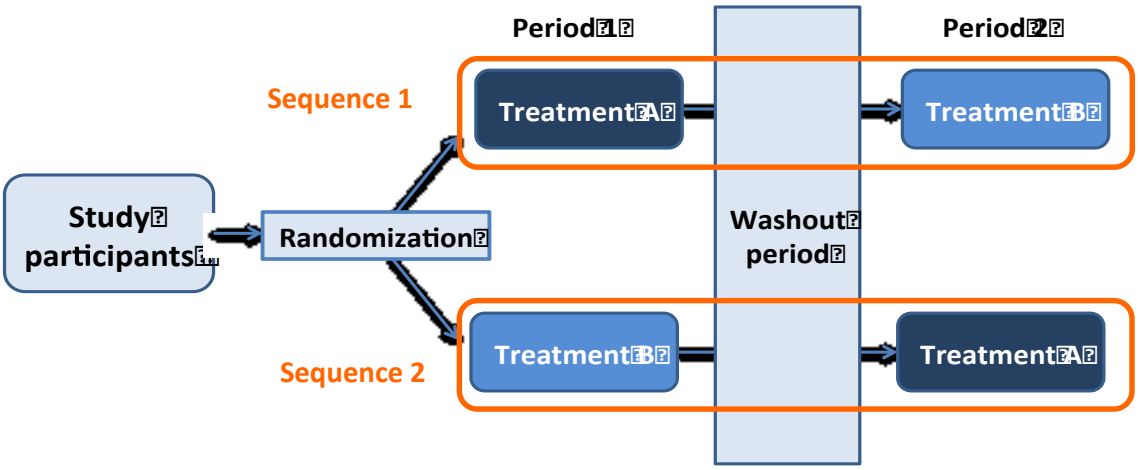
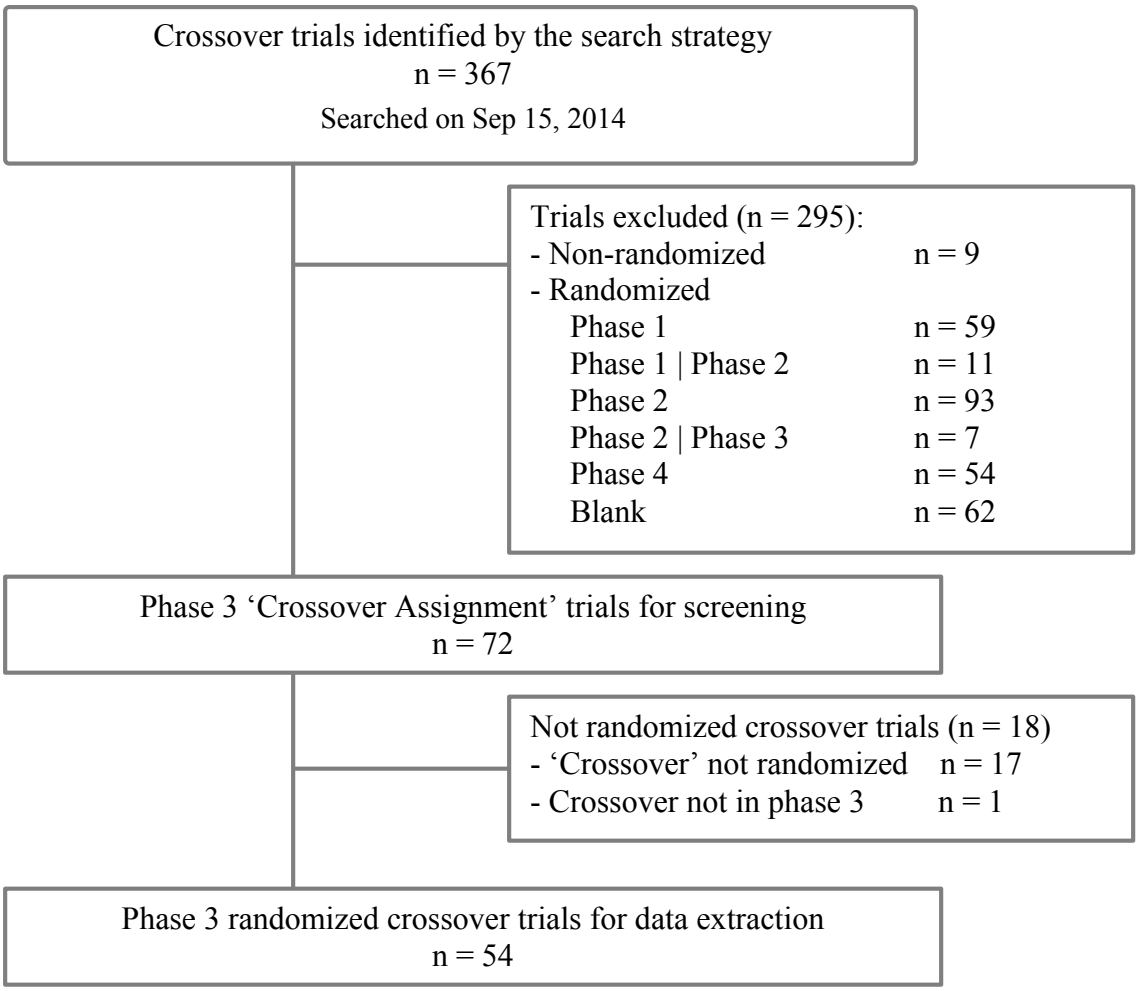


**Figure 2. Flow chart of selected trials**



n of arms/interventions i

| Arms | Assigned Interventions |
| --- | --- |
| Experimental: Treatment Sequence A<br>Rizatriptan - Rizatriptan - Placebo | Drug: rizatriptan<br>Single dose of 10 mg orally disintegrating tablet at onset of migraine attack<br>Drug: Comparator: Placebo<br>Placebo to Rizatriptan |
| Experimental: Treatment Sequence B<br>Rizatriptan - Placebo - Rizatriptan | Drug: rizatriptan<br>Single dose of 10 mg orally disintegrating tablet at onset of migraine attack<br>Drug: Comparator: Placebo<br>Placebo to Rizatriptan |
| Experimental: Treatment Sequence C<br>Placebo - Rizatriptan - Rizatriptan | Drug: rizatriptan<br>Single dose of 10 mg orally disintegrating tablet at onset of migraine attack<br>Drug: Comparator: Placebo<br>Placebo to Rizatriptan |
| Baseline Phase<br>Sumatriptan | Drug: Comparator: Sumatriptan<br>single dose of generic sumatriptan 100 mg at onset of migraine attack |

tan' as an arm, which we would suggest excluding

to specify sequences to be compared in a trial. In

n of arms/interventions in t

| Arms | Assigned Interventions |
| --- | --- |
| Experimental: B16 Arg/Arg<br>B16 Arg/Arg genotype Sequence 1: inhaled salmeterol + inhaled beclomethasone hydroflouroalkane (HFA), followed by inhaled placebo salmeterol + inhaled beclomethasone HFA Sequence 2: inhaled placebo salmeterol + inhaled beclomethasone HFA, followed by inhaled salmeterol + inhaled beclomethasone HFA | Drug: salmeterol<br>50 micrograms (mcg) twice per day (BID) (Serevent 50 mcg diskus, GlaxoSmithKline (GSK), North Carolina)<br>Other Name: Serevent<br>Drug: beclomethasone HFA<br>240 mcg beclomethasone HFA (QVAR, Teva Pharmaceutical Industries)<br>Other Name: QVAR |
| Experimental: B16 Gly/Gly<br>B16 Gly/Gly genotype Sequence 1: inhaled salmeterol + inhaled beclomethasone HFA, followed by inhaled placebo salmeterol + inhaled beclomethasone HFA Sequence 2: inhaled placebo salmeterol + inhaled beclomethasone HFA, followed by inhaled salmeterol + inhaled beclomethasone HFA | Drug: salmeterol<br>50 micrograms (mcg) twice per day (BID) (Serevent 50 mcg diskus, GlaxoSmithKline (GSK), North Carolina)<br>Other Name: Serevent<br>Drug: beclomethasone HFA<br>240 mcg beclomethasone HFA (QVAR, Teva Pharmaceutical Industries)<br>Other Name: QVAR |

**Note: The objective of this trial is to compare treatment effects between two popula crossover-design is set within each population. The two arms are used for registerin presentation and explanation was not clear enough to clarify the exact comparison a subpopulations or two crossover sequences within each subpopulations.**

tion of arms/interventions i

| Arms | Assigned Interventions |
| --- | --- |
| Experimental: Crossover Sequences<br>Sequence 1: fluticasone propionate + montelukast, followed by fluticasone propionate + salmeterol, followed by fluticasone propionate + montelukast<br>Sequence 2: fluticasone propionate, followed by fluticasone + salmeterol, followed by fluticasone propionate + montelukast<br>Sequence 3: fluticasone propionate + salmeterol, followed by fluticasone propionate + montelukast, followed by fluticasone propionate<br>Sequence 4: fluticasone propionate + montelukast, followed by fluticasone propionate + salmeterol, followed by fluticasone propionate<br>Sequence 5: fluticasone propionate + salmeterol, followed by fluticasone propionate, followed by fluticasone propionate + montelukast<br>Sequence 6: fluticasone propionate, followed by fluticasone propionate + montelukast, followed by fluticasone propionate + salmeterol | Drug: fluticasone propionate + montelukast<br>Dry-powder inhaler fluticasone 100 mcg bid (Flovent Diskus®, GlaxoSmithKline) plus Montelukast 5 or 10 mg qd (Singulair®, Merck)<br>Other Name: Flovent Diskus® + Singulair®<br>Drug: fluticasone propionate<br>Dry-powder inhaler fluticasone 250 mcg bid (Flovent Diskus®, GlaxoSmithKline)<br>Other Name: Flovent Diskus®<br>Drug: fluticasone propionate + salmeterol<br>Dry-powder inhaler fluticasone + salmeterol combination 100 mcg/50 mcg bid (Advair Diskus®, GlaxoSmithKline)<br>Other Name: Advair Diskus® |

**Note: This trial uses a complete block, three-treatment, three-period crossover design. Every**
**same interventions but in different orders. We suggest that the six arms should be specified in**
**registration system instead of piling in the same cell, and using the 'cross-reference' function**
**the assigned interventions for each arm accordingly, which would result in six rows in the arm**
**each row representing one arm only.**

**Detailed Description:**

**Note: The 'Participant Flow' section is designed to show how participants progress through the phases of time components need to be specified in the title of the 'Participant Flow' section. We suggest that the 'Pr Randomization' row should be removed from 'Reporting Groups' and use the period specification functi of subsequent tables to specify a 'Pre-Randomization' period.**

**ups' in 'Participant Flow'**

| Reporting Groups | Description |
|---|---|
| **Pre-Randomization** | Participants were enrolled and received BeneFix (recombinant coagulation factor IX) as intravenous (IV) bolus infusion in the first on-demand (OD1) period but were never randomized. |
| **BeneFIX OD1, Then 100 IU/kg, Then OD2, Then 50 IU/kg** | BeneFIX recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 0 international units per kilogram (IU/kg) once per week (QW) for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 50 IU/kg twice weekly (BW) for 16 weeks prophylactically. Dosage form: IV bolus infusion. |
| **BeneFIX OD1 Then 50 IU/kg, Then OD2, Then 100 IU/kg** | BeneFIX recombinant coagulation factor IX) on-demand for 16 weeks (OD1), followed by 50 IU/kg BW for 16 weeks prophylactically, followed by 8 weeks BeneFIX on-demand (OD2), followed by 100 IU/kg QW for 16 weeks prophylactically. Dosage form: IV bolus infusion. |

**Reporting Groups**

| | Description |
|---|---|
| **Rizatriptan / Rizatriptan / Placebo** | Each patient was randomized to receive one of 3 treatment sequences. Three qualifying migraines were then treated based on the prescribed sequence. Two migraine attacks were treated with rizatriptan and one with placebo.<br>The first migraine was treated with Rizatriptan 10 mg Orally Disintegrating Tablet (ODT); the second migraine with Rizatriptan 10 mg ODT; the third migraine with placebo. |
| **Rizatriptan / Placebo / Rizatriptan** | Each patient was randomized to receive one of 3 treatment sequences. Three qualifying migraines were then treated based on the prescribed sequence. Two migraine attacks were treated with rizatriptan and one with placebo.<br>The first migraine was treated with Rizatriptan 10 mg ODT; the second migraine with placebo; and the third migraine with Rizatriptan 10 mg ODT. |
| **Placebo / Rizatriptan / Rizatriptan** | Each patient was randomized to receive one of 3 treatment sequences. Three qualifying migraines were then treated based on the prescribed sequence. Two migraine attacks were treated with rizatriptan and one with placebo.<br>The first migraine was treated with Placebo; the second migraine with Rizatriptan 10mg ODT; and the third migraine with Rizatriptan 10 mg ODT |
| **Sumatriptan 100 mg** | Pre-Randomization Phase conducted 2 months prior to Study Randomization. Eligible participants were to treat a moderate/severe migraine attack with sumatriptan 100 mg. Those who failed to respond to sumatriptan (i.e. continued to experience moderate or severe pain at 2 hours post dose) were classified as non-responders and were entered into the double-blind treatment phase of the study. |

**‘Participant Flow’ in tria**

Participant Flow for 2 periods

Period 1: Baseline Phase

| | Rizatriptan / Rizatriptan / Placebo | Rizatriptan / Placebo / Rizatriptan | Placebo / Rizatriptan / Rizatriptan | Sumatriptan 100 mg |
|---|---|---|---|---|
| STARTED | 0 | 0 | 0 | 194 |
| COMPLETED | 0 | 0 | 0 | 109 |
| NOT COMPLETED | 0 | 0 | 0 | 85 |
| Did not meet Randomization Criteria | 0 | 0 | 0 | 85 |

Period 2: Treatment Phase

| | Rizatriptan / Rizatriptan / Placebo | Rizatriptan / Placebo / Rizatriptan | Placebo / Rizatriptan / Rizatriptan | Sumatriptan 100 mg |
|---|---|---|---|---|
| STARTED | 37 [1] | 36 [1] | 36 [1] | 0 |
| COMPLETED | 33 [2] | 32 [2] | 35 [2] | 0 |
| NOT COMPLETED | 4 | 4 | 1 | 0 |
| Lost to Follow-up | 2 | 3 | 1 | 0 |
| Lack of Qualifying Event | 2 | 1 | 0 | 0 |

[1] Participants who were randomized into the treatment phase

[2] Participants who treated 3 acute migraine attacks with study medication during the treatment phase

**Note: It is helpful to show participant flow after administering ‘Sumatriptan’ in the ‘Ba**
**However, the flow through the three periods in the treatment phase is not specified. We**
**presentation would be to provide participant flow through each period by providing tw**
**treatment periods as: ‘Period 2: Treatment phase I’, ‘Period 3: Treatment phase II’, an**
**respectively.**

Participant Flow' in tri

period the participants were lost to follow-up. W
reporting groups by assigned sequences and pr
'.

Reporting Groups

| | Description |
|---|---|
| All Participants | All participants randomized into the six-sequence crossover study. All TALC participants underwent three 16-week treatment periods:<br>• tiotropium bromide inhalation powder 18 mcg once daily (Tio) plus beclomethasone dipropionate 80 mcg twice daily (1xICS)<br>• salmeterol xinafoate inhalation powder 50 mcg twice daily (LABA) plus beclomethasone dipropionate 80 mcg twice daily (1xICS)<br>• beclomethasone dipropionate 160 mcg twice daily (2xICS) |

Participant Flow: Overall Study

| | All Participants |
|---|---|
| STARTED | 210 |
| COMPLETED | 174 |
| NOT COMPLETED | 36 |

Reporting Groups

| | Description |
|---|---|
| Tapentadol | Subjects treated in the Tapentadol Immediate Release (IR) Open-Label period (followed by randomization to double-blind crossover maintenance period in which all subjects received both IR and ER formulations) |

Measured Values

| | Tapentadol |
|---|---|
| Number of Participants Analyzed [units: participants] | 60 |
| The Difference in the Mean Average Pain Intensity Score on an 11-point Numerical Rating Scale (NRS) During the Last 3 Days of Each Double-blind Treatment Period. (Difference Between Two DB Randomization Treatment Sequences) [units: Units on a scale] Least Squares Mean ( 95% Confidence Interval ) | 0.1 ( -0.09 to 0.28 ) |

**Note: The goal of this trial was to compare different formulations of the same-ingredient (Tapentadol IR formu**
**Tapentadol ER formulation). Instead of grouped in one 'Tapentadol', we suggest that registering the original a**
**measurements grouped by different sequences with period-specific measured values if available, would have be**
**informative.**

**ups' for 1st primary outc**

**Figure 10. Comparison of registration for arms/interventions in parallel-design and crossover-design trial**

- For parallel-design trial

| Arms | Assigned Interventions |
|---|---|
| Experimental: A<br>(Description for A) | Drug: A<br>(Key details of Intervention A) |
| Experimental: B<br>(Description for B) | Drug: B<br>(Key details of Intervention B) |

- For crossover-design trial

| Arms | Assigned Interventions |
|---|---|
| Experimental: A first, then B<br>(Description for sequence 1) | Drug: A<br>Drug: B |
| Experimental: B first, then A<br>(Description for sequence 2) | Drug: A<br>Drug: B |

**Figure 11. Illustration of proposed way of registering 'Participant Flow'**

**Reporting Groups**

| | Description |
|---|---|
| **Sequence 1 -- A first then B** | … |
| **Sequence 2 -- B first then A** | … |

**Participant Flow for 2 periods**

**Period 1: Treatment Period I**

| | Sequence 1 – A first then B | Sequence 2 – B first then A |
|---|---|---|
| **STARTED** | $N_1$ | $N_2$ |
| **COMPLETED** | … | … |
| **NOT COMPLETED** | … | … |

**Period 2: Treatment Period II**

| | Sequence 1— A first then B | Sequence 2 – B first then A |
|---|---|---|
| **STARTED** | $N_3$ | $N_4$ |
| **COMPLETED** | … | … |
| **NOT COMPLETED** | … | … |

**Figure 12. Illustration of proposed way of registering 'Baseline Characteristics'**

**Reporting Groups**

| | Description |
|---|---|
| **Total Population / Overall Study Population** | |
| **Sequence 1 -- A first then B** | … |
| **Sequence 2 -- B first then A** | … |

**Baseline Measures**

| | Total Population / Overall Study Population | Sequence 1 – A first then B | Sequence 2 – B first then A |
|---|---|---|---|
| **Number of Participants [units: participants]** | N | $N_1$ | $N_2$ |
| **Age …** | … | … | … |

**Figure 13. An illustrative example for registering continuous outcome for a two-intervention two periods crossover design trial**

**Reporting Groups**

| | Description |
|---|---|
| **Sequence 1 -- A first then B** | … |
| **Sequence 2 -- B first then A** | … |

**Measured Values**

| | Sequence 1 – A first then B | Sequence 2 – B first then A |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | $N_1$ | $N_2$ |
| **Outcome Measurement 1¶** | | |
| **Baseline Measurement§** | … | … |
| **Value from Period 1** | … | … |
| **Value from Period 2** | … | … |
| **Within-individual difference#** | … | … |

¶: 'Outcome Measurement 1' refers to 'Measure Title'
§: (Optional). Whether it is need to specify 'Baseline Measurement' depends on the context and specific measurement of the trial.
#:'Within-individual difference' can be changed based on how data were to analyze.

**Figure 14. An illustrative example for registering binary outcome for a two-intervention two periods crossover design trial**

**Reporting Groups**

| | Description |
|---|---|
| **Sequence 1 -- A first then B** | … |
| **Sequence 2 -- B first then A** | … |

**Measured Values**

| | Sequence 1 – A first then B | Sequence 2 – B first then A |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | $N_1$ | $N_2$ |
| **Outcome Measurement 1¶** | | |
| **Baseline Measurement §** | … | … |
| **(0, 0) ♯** | … | … |
| **(0, 1)** | … | … |
| **(1, 0)** | | |
| **(1, 1) ♯** | … | … |

¶: 'Outcome Measurement 1' refers to 'Measure Title'
§: (Optional). Whether it is needed to specify 'Baseline Measurement' depends on the context and specific measurement of the trial.
♯: Optional for concordant counts. Whether it is needed to specify has to deal with how data is aggregated and analyzed.

gistering time-to-event d

1. Primary: Time to Progression [ Time Frame: 36 months ]

Hide Outcome Measure 1

| | |
|---|---|
| **Measure Type** | Primary |
| **Measure Title** | Time to Progression |
| **Measure Description** | Time to progression is defined as follows: if the PSA returns to baseline (defined as the PSA value prior to starting leuprolide or goserelin) or increases to the absolute value of 5 ng/ml. |
| **Time Frame** | 36 months |
| **Safety Issue** | No |

**Population Description**

| **Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.** |
|---|
| Per protocol. First intervention phase-73 participants (thalidomide) were analyzed and 0 was excluded; 74 participants were analyzed (placebo) and 1 was excluded for discrepancy in data entry. Crossover phase-50 participants were analyzed (thalidomide)and 1 was excluded for discrepancy in data entry, 38 participants for placebo and 0 excluded. |

**Reporting Groups**

| | **Description** |
|---|---|
| **Thalidomide** | Participants who received thalidomide in period 1 or 2. |
| **Placebo** | Participants who received placebo in period 1 or 2 |

**Measured Values**

| | **Thalidomide** | **Placebo** |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **123** | **112** |
| **Time to Progression [units: months] Median ( 95% Confidence Interval )** | **15 ( 12.0 to 22.1 )** | **9.6 ( 8.5 to 12.9 )** |

**No statistical analysis provided for Time to Progression**

asured values from sev

Measured Values

| | Vyvanse | Placebo |
|---|---|---|
| Number of Participants Analyzed [units: participants] | 113 | 113 |
| Onset of Effect of Vyvanse [units: scores on a scale] Least Squares Mean ± Standard Error | | |
| 1.5 hours | 0.70 ± 0.09 | 1.14 ± 0.09 |
| 2.5 hours | 0.45 ± 0.09 | 1.42 ± 0.09 |
| 5 hours | 0.44 ± 0.10 | 1.60 ± 0.10 |
| 7.5 hours | 0.54 ± 0.09 | 1.56 ± 0.09 |
| 10 hours | 0.60 ± 0.09 | 1.43 ± 0.09 |
| 12 hours | 0.90 ± 0.10 | 1.41 ± 0.10 |
| 13 hours | 1.05 ± 0.10 | 1.31 ± 0.10 |

**Appendix 1**

Search syntax (367 studies were found on September 15, 2014)

"Crossover Assignment" [DESIGN-INTERVENTION-MODEL] AND NOT NOTEXT [CITATIONS] AND NOT NOTEXT [FIRST-RECEIVED-RESULTS-DATE]

ID: NCT__ __ __ __ __ __ __ __

## Appendix 2. Data Abstraction Form for Crossover Trials

**Purpose:**
This form is designed for assessing the study design, analysis and reporting of phase 3 crossover trials registered on ClinicalTrials.gov.

**Instruction:**
- Italic text section provides instructions for how each question. Use the tree-structure instruction after each question to help you locate the data fields.
*[Section]* → *[Sub-section]* → *[Sub-Subsection]*
- * mark before each question indicates that data for this question can be extracted directly from ClinicalTrials.gov, and will not need to extract on electronic form.

**Completed by whom:**
Two independent data extractors.

*1. Please enter the 11-character ClinicalTrials.gov registration number, beginning with NCT:
N C T __ __ __ __ __ __ __ __

*From questions 2 through 20, please refer to **[Full Text View]** on ClinicalTrials.gov. (For question 3, please also refer to **[Tabular View]**).*


2. Look at the 'Study Design' section of the [Full text view]. Is "Crossover Assignment" selected for "Intervention Model'?
*[Full Text View]* → *[Purpose]* →*[Study Design]*
( 1) Yes
( 2) No *(Stop and inform Lijuan Zeng: lzeng3@jhu.edu)*

3. Look at the 'Purpose', 'Detailed Description' (if available) and 'Arms' sections of the [Full Text View], as well as the 'Brief Summary' and the 'Detailed Description' of the [Tabular View]. In your opinion, does this registration describe a phase 3 randomized crossover trial?
*[Full Text View]* → *[Purpose]* → *[Detailed Description] (Note: some studies may not have 'detailed description' next to the 'Arms' table)*
( 1) Yes *(Skip to 5)*
( 2) No (*Continue to 4)*
( 3) Cannot tell *(Stop and inform Lijuan Zeng: lzeng3@jhu.edu)*
*Randomized crossover trial: a clinical trial in which groups of participants are randomized to receive two or more interventions in a particular order.*

4. Why do you think this is not a phase 3 randomized crossover trial?
( 1) The 'crossover' is not randomized (see example below).
( 2) The study had multi-phases (e.g., phases 2 and 3) and the 'crossover' is not in phase 3.
( 3) Cannot tell *(Stop and inform Lijuan Zeng: lzeng3@jhu.edu)*
*(Example: If the crossover is described as "participants were offered the option to cross over to X treatment", the crossover in the trial was not randomized.)*

5. Based on 'Purpose' and/or 'Detailed Description' (if available), is a washout period included in this trial? *(A washout period can be described in text, or reported in a tabular format)*
( 1) Yes.
( 2) No.
( 3) Cannot tell.
*The washout period is the interval of time considered necessary for a biological system to remove a foreign substance and to be free of its influence.*

*6. What is the registered 'Endpoint classification/Study Classification'?
*[Full Text View] → [Purpose] → [Study Design] → [Endpoint Classification/Study Classification]*
( 1) Not reported
( 2) Safety Study
( 3) Efficacy Study
( 4) Safety/Efficacy Study
( 5) Bio-equivalence Study
( 6) Bio-availability Study
( 7) Pharmacokinetics Study
( 8) Pharmacodynamics Study
( 9) Pharmacokinetics/dynamics Study
( 10) Others, please specify, a: _____

*7. What is the registered 'Primary Purpose' under the 'Study Design'?
*[Full Text View] → [Purpose] → [Study Design] → [Primary Purpose]*
( 1) Treatment
( 2) Prevention
( 3) Diagnostic

*8. How is 'Masking' registered?
*[Full Text View] → [Purpose] → [Study Design] → [Masking]*
( 1) Open-label *(Skip to 10)*
( 2) Single blind
( 3) Double blind

*9. Based on the registration, which of the following parties are masked in the 'single-blind' or 'double-blind' design? *(Check all that apply)*
*[Full Text View] → [Purpose] → [Study Design] → [Masking]*

| Yes | No | |
|---|---|---|
| ( 1) | ( 2) | a. Subject |
| ( 1) | ( 2) | b. Caregiver |
| ( 1) | ( 2) | c. Investigator |
| ( 1) | ( 2) | d. Outcomes Assessor |
| ( 1) | ( 2) | e. Not reported |

*10. What are the registered the 'Intervention' types under 'Intervention'? *(Check all that apply)*
*[Full Text View]* → *[Purpose]* → *[Intervention]*

| Yes | No | |
|---|---|---|
| ( 1) | ( 2) | a. Drug |
| ( 1) | ( 2) | b. Device |
| ( 1) | ( 2) | c. Biological/Vaccine |
| ( 1) | ( 2) | d. Procedure/Surgery |
| ( 1) | ( 2) | e. Behavioral |
| ( 1) | ( 2) | f. Dietary Supplement |
| ( 1) | ( 2) | g. Other. Please specify: h:_____ |

*For question 11 to 13, please refer to the 'Arms', 'Assigned interventions' and 'Intervention' cells of the [Full Text View].*
*[Full Text View]* → *[Purpose]* → *[Arms], [Assigned Interventions] & [Intervention]*

11. Based on the information presented in these cells, in your opinion, how many interventions are compared in the trial? *(Indicate the number of interventions compared in the crossover phase, excluding interventions used only in the run-in period, washout period, run-out period, and standard of care given to participants for the entire study period)*
( 1) 2
( 2) 3
( 3) 4
( 4) 5
( 5) 6
( 6) > 6, please specify the number of compared interventions, a: _____
( 7) Cannot tell
*(Please refer to examples in the Appendix 3)*

12. How many treatment periods are registered? *(Indicate the number of periods in which interventions are compared, excluding run-in periods, washout periods, and run-out periods)*
( 1) 2
( 2) 3
( 3) 4
( 4) 5
( 5) 6
( 6) > 6. Please specify the number of periods, a: _____
( 7) Cannot tell
*(Please refer to examples in the Appendix 3)*

13. How many sequences are registered? *(Indicate the number of periods in which interventions are compared, excluding run-in periods, washout periods, and run-out periods)*
( 1) 2
( 2) 3
( 3) 4
( 4) 5
( 5) 6
( 6) > 6. Please specify the number of compared interventions, a: _____
( 7) Cannot tell

14. What are the registered sequences?
( 1) AB|BA
( 2) ABAB|BABA
( 3) ABA|BAB
( 4) ABC|ACB|BAC|BCA|CBA|CAB
( 5) Other sequence design. Please specify, a: _____
_____
*e.g.: AB|BA; ABC|BCA|CBA; ABAB|BABA; ABC|ACB|BCA|BAC|CAB|CBA etc.*
*(Use different alphabetic letters for different interventions; separate sequences with '|')*

15. How are the 'Arms' registered? *(Check all that apply)*
*[Full Text View]* → *[Purpose]* → *[Arms]*

| Yes | No | |
|---|---|---|
| ( 1) | ( 2) | a. By Sequence |
| ( 1) | ( 2) | b. By Intervention |
| ( 1) | ( 2) | c. By Period |
| ( 1) | ( 2) | d. Others. Please specify. f: _____ |
| ( 1) | ( 2) | e. Cannot tell |

*(Please refer to examples in the Appendix 3)*

*16. Please copy and paste the information provided in the 'Arm' column into the textbox below (one row for one arm):

| |
|---|
| |

17. Based on questions 15 and 16, in your opinion, does the trial registration of the 'Arms' account for the crossover design?
( 1) Yes.
( 2) No. Please specify why, a: _____
( 3) Cannot tell. Please specify why, b:_____

18. How is the information in 'Assigned Interventions' columns presented?
*[Full Text View]* → *[Purpose]* → *[Assigned Interventions]*
( 1) Treatment details in 'Assigned interventions' cells are the same for all rows.
( 2) Treatment details in 'Assigned interventions' cells are not the same for all rows.
( 3) Others. Please specify. a: _____
*(Please refer to examples in the Appendix 3)*

*19. Please copy and paste the information provided in the 'Assigned intervention' column into the textbox below (one row for one arm):

| |
|---|
| |

20. Based on questions 18 and 19, in your opinion, does the trial registration of the 'Assigned Interventions' account for the crossover design?
( 1) Yes.
( 2) No. Please specify why, a: _____
( 3) Cannot tell. Please specify why, b:_____

*From questions 21 through 41, please refer to **[Study Results]** tab on ClinicalTrials.gov.*

Questions 21-24 refer to the 'Participant Flow' section of the [Study Results]


21. Look at the 'Participant Flow' table. In your opinion, how many treatment periods are registered?
*(Indicate the number of periods in which interventions are compared, excluding run-in periods, washout periods, and run-out periods.)*
( 1) 2
( 2) 3
( 3) 4
( 4) 5
( 5) 6
( 6) > 6. Please specify the number of periods, a: _____
( 7) Cannot tell

22. How are the 'Reporting Groups' presented? *(Check all that apply)*
*[Study Results]* → *[Participant Flow]* → *[Reporting Groups]*
Yes No
( 1) ( 2) a. By Sequence
( 1) ( 2) b. By Intervention
( 1) ( 2) c. By Period
( 1) ( 2) d. Others. Please specify, f: _____
( 1) ( 2) e. Cannot tell
*(Please refer to examples in the Appendix 3)*

23. How are the 'Participant Flow' tables presented?
( 1) One table only for Overall Study / Total population / All participants.
( 2) Separate tables by Period, without pre-randomization and/or washout periods
( 3) Separate tables by Period, with pre-randomization and/or washout periods
( 4) Others. Please specify, a: _____
( 5) Cannot tell
*(Please refer to examples in the Appendix 3)*

24. Based on questions 21 to 23, in your opinion, does the registration of the 'Participant Flow' account for the crossover design?
( 1) Yes.
( 2) No. Please specify why, a: _____
( 3) Cannot tell. Please specify why, b:_____

*For question 25, please refer to the 'Baseline Characteristics' section of the [Study Results].*
25. How are the 'Reporting Groups' presented? *(Check all that apply)*
*[Study Results]* → *[Baseline Characteristics]* → *[Reporting Groups]*
Yes No
( 1) ( 2) a. By Total
( 1) ( 2) b. By Sequence
( 1) ( 2) c. By Intervention
( 1) ( 2) d. By Period
( 1) ( 2) e. Others. Please specify, f: _____

*For question 26, please refer to the 'Outcome Measures' section of the [Study Results]*
26. How many primary outcomes are registered?
( 1) 1
( 2) 2
( 3) 3
( 4) More than 3. Please specify the total number, a: _____

ID: NCT__ __ __ __ __ __ __ __

ID: NCT__ __ __ __ __ __ __ __

*For question 27 to 41, please refer to the first listed primary outcome of [Study Results] page. [Study Results] → [Outcome Measures] → [1. Primary: ...]*

27. What is the title of the 1st primary outcome?
*(Please copy and paste the description in the 'Measure Title' under '1. Primary')*

---

*(Please refer to examples in the Appendix 3)*

28. In your opinion, what is the outcome type for the 1st primary outcome?
( 1) Continuous outcome *(Skip to 30)*
( 2) Categorical outcome *(Skip to 30)*
( 3) Time-to-event outcome *(Continue to 29)*
( 4) Others. Please specify: a: _____ *(Skip to 30)*
( 5) Cannot Tell. *(Skip to 30)*

29. For Time-to-Event outcome, how is the outcome registered?
( ) Reported as continuous data (e.g.: mean time to event with measure of dispersion)
( ) Reported as categorical data at different time points by arm or comparison group

30. After looking at 'Measure Title', 'Measure Description' and 'Measured Values', what is the specific metric for the 1st primary outcome?
( 1) Value at a time-point
( 2) Time-to-event
( 3) Change from the baseline before randomization
( 4) Change from the period-baseline (i.e.: change from baseline of period 2)
( 5) Within-individual difference between values at the end of each period
( 6) Within-individual difference between changes from baseline
( 7) Within-individual indicator of concordant versus discordant events between periods
( 8) Others. Please specify, a: _____
( 9) Cannot tell
*The 'specific metric' is the format of the outcome data from each participant that is used for analysis*

31. Based on the 'Measured Values', what is the method of aggregation for the 1st primary outcome?
( 1) Number
( 2) Mean
( 3) Median
( 4) Least Squares Mean
( 5) Geometric Means
( 6) Log Mean
( 7) Proportion/percent
( 8) Others. Please specify, a: _____
( 9) Cannot tell
*The 'method of aggregation' is how data from each group is summarized under 'Measured Values'*

32. Based on the 'Time Frame' information, in your opinion, does the 'Time Frame' for the 1st primary outcome includes all randomized periods?
*[Study Results] → [Outcome Measures] → [1. Primary: ...] → [Time Frame]*
( 1) Yes.
( 2) No. Please specify why, a: _____
( 3) Cannot tell. Please specify why, b:_____

33. Based on the 'Time Frame' information, in your opinion, data from which periods are used for analyzing the primary outcome?
( 1) Data from all periods
( 2) Data from first period only
( 3) Data from more than one period but not all periods
( 4) Others. Please specify, a: _____
( 5) Cannot tell

34. Based on questions 27 to 33, is the definition for the 1st primary outcome appropriate for the crossover design?
( 1) Yes.
( 2) No. Please specify why, a: _____
( 3) Cannot tell. Please specify why, b:_____
*(Please refer to examples in the Appendix 3)*

35. What is the registered 'Analysis Population'? *(Described in the 'Population Description') (Check all that apply)*

| Yes | No | |
|---|---|---|
| ( 1) | ( 2) | a. ITT (Intention-To-Treat) |
| ( 1) | ( 2) | b. Per-protocol |
| ( 1) | ( 2) | c. As treated |
| ( 1) | ( 2) | d. mITT (modified Intention-To-Treat) |
| ( 1) | ( 2) | e. FAS (Full Analysis Set) |
| ( 1) | ( 2) | f. Others. Please specify, h: _____ |
| ( 1) | ( 2) | g. Not reported *(Skip to 37)* |

*36. Please copy and paste the information provided in the 'Population Description' section into the textbox below:

37. How are the 'Reporting Groups' presented? *(Check all that apply)*
*[Study Results] → [Outcome Measures] → [1. Primary: ...] → [Reporting Groups]*

| Yes | No | |
|---|---|---|
| ( 1) | ( 2) | a. By Total |
| ( 1) | ( 2) | b. By Sequence |
| ( 1) | ( 2) | c. By Intervention |
| ( 1) | ( 2) | d. By Period |
| ( 1) | ( 2) | e. Others. Please specify, f: _____ |

38. Based on the 'Measured Values', are the results presented by period?
*[Study Results] → [Outcome Measures] → [1. Primary: ...] → [Measured Values]*
( 1) Yes.
( 2) No.
( 3) Cannot tell. Please specify, a:_____
*(Please refer to examples in the Appendix 3)*

39. Is a description of the 'Statistical analysis' provided after the 'Measured Values' section?
( 1) Yes *(Continue to 40)*
( 2) No *(Skip to 41)*
( 3) Cannot tell
*(Please refer to examples in the Appendix 3)*

*40. Based on 'Method' information in 'Statistical Analysis', what is/are the registered statistical method(s) for estimation? *(Check all that apply)*

| Yes | No | |
|---|---|---|
| ( 1) | ( 2) | a. ANCOVA |
| ( 1) | ( 2) | b. ANOVA |
| ( 1) | ( 2) | c. Chi-squared test |
| ( 1) | ( 2) | d. Chi-squared test, Corrected |
| ( 1) | ( 2) | e. Cochran-Mantel-Haenszel |
| ( 1) | ( 2) | f. Fisher Exact |
| ( 1) | ( 2) | g. Kruskal-Wallis |
| ( 1) | ( 2) | h. Log Rank |
| ( 1) | ( 2) | i. Mantel Haenszel |
| ( 1) | ( 2) | j. McNemar |
| ( 1) | ( 2) | l. Mixed Models Analysis |
| ( 1) | ( 2) | m. Regression, Cox |
| ( 1) | ( 2) | n. Regression, Linear |
| ( 1) | ( 2) | o. Regression, Logistic |
| ( 1) | ( 2) | p. Sign test |
| ( 1) | ( 2) | q. t-test, 1 sided |
| ( 1) | ( 2) | r. t-test, 2 sided |
| ( 1) | ( 2) | u. Wilcoxon (Mann-Whitney) |
| ( 1) | ( 2) | v. Other(s). Please specify, w:_____ |

41. Based on questions from 27 to 40, in your opinion, does the registration of the results of the 1st primary outcome account for the crossover design?
( 1) Yes.
( 2) No. Please specify why, a: _____
( 3) Cannot tell. Please specify why, b: _____

**"Adverse Events"**
*For questions 42 and 43, please refer to **'Serious Adverse Events'** and/or '**Other Adverse Events'** sections.*

42. Are there any adverse events registered?
( 1) Yes.
( 2) No. *(Skip to 44)*
( 3) Cannot tell

43. How are the adverse events 'Reporting Groups' presented? *(Check all that apply)*
*[Study Results] → [Serious Adverse Events] or [Other Adverse Events]*

| Yes | No | |
|---|---|---|
| ( 1) | ( 2) | a. By Total |
| ( 1) | ( 2) | b. By Sequence |
| ( 1) | ( 2) | c. By Intervention |
| ( 1) | ( 2) | d. By Period |
| ( 1) | ( 2) | e. Others. Please specify, f: _____ |

**Review of the entire registration**
44. Any comments you may have (Type "None" if you don't have any comments)
_____
_____
_____

**Administrative Information**
45. Form Completed Date (MM/DD/YYYY): __ __ / __ __ / __ __ __ __

46. Initials of the data abstractor: __ __

47. Name of the data abstractor: _____ _____
First Last

## Appendix 3. Examples for using 'Data Abstraction Form for Crossover Trials'

**Purpose:**
The following examples are provided to better understand the question options in the data extraction form.

Example for question 11: How many interventions are compared in the trial?
*Example 1:*
*Two interventions are compared in the following study (NCT00090142).*

| Intervention |
|---|
| Drug: Comparator: Montelukast<br>Drug: Comparator: Placebo |

| Arms | Assigned Interventions |
|---|---|
| Experimental: 1<br>Montelukast - Placebo | Drug: Comparator: Montelukast<br>Montelukast 10 mg tablet administered orally as a single witnessed dose before exercise challenge<br>Drug: Comparator: Placebo<br>Placebo tablet administered orally as a single witnessed dose before exercise challenge |
| Experimental: 2<br>Placebo - Montelukast | Drug: Comparator: Montelukast<br>Montelukast 10 mg tablet administered orally as a single witnessed dose before exercise challenge<br>Drug: Comparator: Placebo<br>Placebo tablet administered orally as a single witnessed dose before exercise challenge |

*Example 2:*
*In this study (NCT00004635), although 4 interventions were involved, only Thalidomide and Placebo interventions were compared to one another. (After reading 'Arms' section about study design, we learned that the other 2 drugs were used during run-in or washout periods only). Therefore, we count the compared interventions as 2 for this study.*

| Intervention |
|---|
| Drug: Thalidomide<br>Drug: leuprolide acetate<br>Drug: goserelin<br>Other: Placebo |

| Arms |
|---|
| Experimental: Thalidomide<br>Study participants are randomly assigned to one of two treatment groups. Participants received leuprolide or goserelin for 6 months. In period 1 participants received thalidomide orally 200 mg a day. Patients will be followed until PSA progression defined as prostate-specific antigen (PSA) level that returns to what it was before beginning leuprolide or goserelin or to 5 nanograms per liter, whichever is lower. The participants are returned to the leuprolide or goserelin treatment for 6 months. In period 2 participants received the placebo for thalidomide once a day. |
| Experimental: Placebo<br>Study participants are randomly assigned to one of two treatment groups. Participants received leuprolide or goserelin for 6 months. In period 1 participants received placebo for thalidomide. Patients will be followed until PSA progression defined as prostate-specific antigen (PSA) level that returns to what it was before beginning leuprolide or goserelin or to 5 nanograms per liter, whichever is lower. The participants are returned to the leuprolide or goserelin treatment for 6 months. In period 2 participants received thalidomide 200 mg once a day. |

Example for question 12: How many treatment periods are registered?

*Example:*

*In the following crossover trial (NCT00090142), two sequences were used. We call this an AB|BA sequence.*

| Arms | Assigned Interventions |
|---|---|
| Experimental: 1 Sequence1<br>Montelukast - Placebo | Drug: Comparator: Montelukast<br>Montelukast 10 mg tablet administered orally as a single witnessed dose before exercise challenge<br>Drug: Comparator: Placebo<br>Placebo tablet administered orally as a single witnessed dose before exercise challenge |
| Experimental: 2 Sequence2<br>Placebo - Montelukast | Drug: Comparator: Montelukast<br>Montelukast 10 mg tablet administered orally as a single witnessed dose before exercise challenge<br>Drug: Comparator: Placebo<br>Placebo tablet administered orally as a single witnessed dose before exercise challenge |

Example for question 15: How are the 'Arms' registered?

*Example 1: By Sequence*

| Arms | |
|---|---|
| Experimental: 1<br>Montelukast - Placebo | Sequence 1 |
| Experimental: 2<br>Placebo - Montelukast | Sequence 2 |

*Example 2: By Intervention*

| Arms | |
|---|---|
| Experimental: BAX 326 | Intervention 1 |
| Active Comparator: BeneFIX | Intervention 2 |

Example for question 18: How is the information in 'Assigned Interventions' columns presented?

*Example 1: Option 1. Treatment details in 'Assigned interventions' cells are the same for all rows.*

| Assigned Interventions |
| --- |
| Drug: Comparator: Montelukast<br>Montelukast 10 mg tablet administered orally as a single witnessed dose before exercise challenge<br>Drug: Comparator: Placebo<br>Placebo tablet administered orally as a single witnessed dose before exercise challenge |
| Drug: Comparator: Montelukast<br>Montelukast 10 mg tablet administered orally as a single witnessed dose before exercise challenge<br>Drug: Comparator: Placebo<br>Placebo tablet administered orally as a single witnessed dose before exercise challenge |

*Example 2: Option 2. Treatment details in 'Assigned interventions' cells are not the same for all rows.*

| Assigned Interventions |
| --- |
| Drug: CoenzymeQ10<br>CoenzymeQ10 will be given in 10 mg/kg daily up to 400 mg. Then a draw of CoQ10 troughs every three months will be performed.<br>Other Name: CoenzymeQ10 |
| Drug: Placebo<br>Placebo will be given in 10 mg/kg daily up to 400 mg. Then a draw of placebo troughs every three months will be performed. This treatment group will be treated as the active group.<br>Other Name: Placebo |

Example for question 22: How are the 'Reporting Groups' presented?
*Example: The trial (NCT00127166) specifies that the 'Reporting Groups' in 'Participant Flow' section in 'by sequence' format, the column names for 'Participant Flow' table will be labeled according to the different sequences.*

**Reporting Groups**

| | Description |
|---|---|
| **Montelukast / Salmeterol** | Period I- Montelukast 5 milligrams (mg) oral tablet once daily and Salmeterol matching placebo dry powder inhaler (DPI) twice daily for 4 weeks.<br>Period II- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 micrograms (mcg) twice daily for 4 weeks.<br>Inhaled Fluticasone 100 mcg twice daily throughout the study. |
| **Salmeterol / Montelukast** | Period I- Montelukast matching placebo oral tablet once daily and Salmeterol DPI 50 mcg twice daily for 4 weeks.<br>Period II- Montelukast 5 mg oral tablet once daily and Salmeterol matching placebo DPI twice daily for 4 weeks.<br>Inhaled Fluticasone 100 mcg twice daily throughout the study. |

**Participant Flow for 3 periods**

**Period 1: Period I**

| | Montelukast / Salmeterol | Salmeterol / Montelukast |
|---|---|---|
| **STARTED** | 78 | 76 |
| **COMPLETED** | 75 | 74 |
| **NOT COMPLETED** | 3 | 2 |
| **Protocol Violation** | 0 | 2 |
| **Withdrawal by Subject** | 2 | 0 |
| **Patient did not meet inclusion criteria** | 1 | 0 |

Example for question 23: How are the 'Participant Flow' tables presented?
*Example 1: Trial (NCT00494143) presents one table only titled with 'Overall Study'.*

**Participant Flow: Overall Study**

| | Conventional, Prescribed, CESR | Conventional, CESR, Prescribed | Prescribed, CESR, Conventional | Prescribed, Conventional, CESR |
|---|---|---|---|---|
| **STARTED** | 1 | 2 | 3 | 0 |
| **COMPLETED** | 1 | 2 | 3 | 0 |
| **NOT COMPLETED** | 0 | 0 | 0 | 0 |

*Example 2: Trial (NCT00432744) presents separate tables by Period, without pre-randomization and/or washout periods.*

**Participant Flow for 2 periods**

**Period 1: Months 0-6**

| | Placebo First | CoenzymeQ10 Frist |
|---|---|---|
| STARTED | 12 | 12 |
| COMPLETED | 7 | 8 [1] |
| NOT COMPLETED | 5 | 4 |
| Withdrawal by Subject | 4 | 4 |
| Too disabled to score | 1 | 0 |

[1] One patient in period 1 "other reason" for loss became too disabled to complete the 6 month test.

**Period 2: Months 7 - 12**

| | Placebo First | CoenzymeQ10 Frist |
|---|---|---|
| STARTED | 7 | 8 |
| COMPLETED | 6 | 7 |
| NOT COMPLETED | 1 | 1 |
| Withdrawal by Subject | 1 | 0 |
| Too disabled to score | 0 | 1 |

*Example 3: Trial (NCT00127166) presents separate tables by Period, with one washout period.*

**Period 1: Period I**

| | Montelukast / Salmeterol | Salmeterol / Montelukast |
|---|---|---|
| STARTED | 78 | 76 |
| COMPLETED | 75 | 74 |
| NOT COMPLETED | 3 | 2 |
| Protocol Violation | 0 | 2 |
| Withdrawal by Subject | 2 | 0 |
| Patient did not meet inclusion criteria | 1 | 0 |

**Period 2: Washout Period**

| | Montelukast / Salmeterol | Salmeterol / Montelukast |
|---|---|---|
| STARTED | 75 | 74 |
| COMPLETED | 75 | 73 |
| NOT COMPLETED | 0 | 1 |
| Patient did not meet inclusion criteria | 0 | 1 |

**Period 3: Period II**

| | Montelukast / Salmeterol | Salmeterol / Montelukast |
|---|---|---|
| STARTED | 75 | 73 |
| COMPLETED | 72 | 73 |
| NOT COMPLETED | 3 | 0 |
| Withdrawal by Subject | 2 | 0 |
| Patient did not perform Visit 6 exercise | 1 | 0 |

Example for question 27: What is the title of the 1st primary outcome?

*Example:*

1. Primary: Number of Participants With a Sustained Pain-free (SPF) Response From 2 to 24 Hours Post-dose [ Time Frame: From 2 to 24 hours post-dose. All 3 migraine attacks were to have been treated within 19 weeks of randomization (when study medication was dispensed). ]

| | |
|---|---|
| **Measure Type** | Primary |
| **Measure Title** | Number of Participants With a Sustained Pain-free (SPF) Response From 2 to 24 Hours Post-dose |
| **Measure Description** | SPF 2-24 hours is defined for all participants as having no pain at 2 hours post-dose and without the return of any pain or the use of any rescue medication (any medication taken after the first dose of study medication for any migraine pain or symptoms) from 2-24 hours. |
| **Time Frame** | From 2 to 24 hours post-dose. All 3 migraine attacks were to have been treated within 19 weeks of randomization (when study medication was dispensed). |
| **Safety Issue** | No |

Example for question 34: Is the definition for the 1st primary outcome appropriate for the crossover design?

*Example 1: The definition for the 1st primary outcome is appropriate for the crossover design. The 1st primary outcome in the trial (NCT00432744) is a continuous outcome, GMFM 88. The treatment effect is estimated using within-subject differences between values at the end of period 1 (6 month) and period 2 (12 month), which is an appropriate outcome using crossover design.*

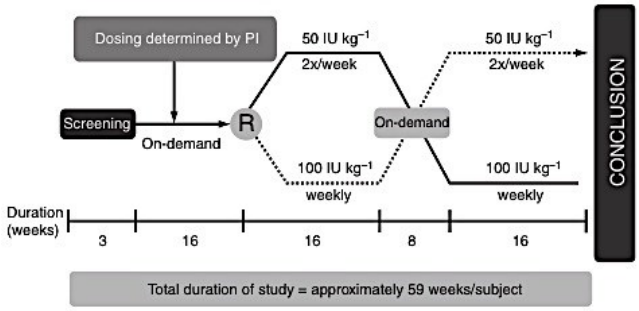
| | |
|---|---|
| **Measure Type** | Primary |
| **Measure Title** | McMaster Gross Motor Function (GMFM 88) |
| **Measure Description** | The McMaster Gross Motor Function is a validated scale ranging from 0 to 100 (the higher the better). Since there was the possibility of a subject becoming totally disabled our FDA peer reviewed design called for its use as follows: If the subject completed both periods, the score was calculated as the difference in scores between the end of Period 2 (at 12 months) minus that at the end of Period 1 (6 months). If a subject became totally disabled, this difference was considered as plus infinity if it occurred in period 1 (Penalizes period 1), and minus infinity if it occurred in Period 2 (Penalizes period 2). The two treatments were compared via the Wilcoxon test, and the effect size was estimated using Kendall's Tau-B. This is interpreted in a similar manner to correlation with positive values favoring COQenzyme10 and negative values favoring placebo. One of the links in this report is to the the GMFM scale and how it is scored. A link to the instrument is included. |
| **Time Frame** | Taken at 6 and 12 Months |
| **Safety Issue** | No |

**Measured Values**

| | Placebo First | CoenzymeQ10 Frist |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **6** | **8** |
| **McMaster Gross Motor Function (GMFM 88) [units: units on a scale] Median ( Inter-Quartile Range )** | **-0.002 ( -0.47 to 1.36 )** | **-0.12 ( -2.75 to 1.75 )** |

*Example 2: The definition for the 1st primary outcome is not appropriate for the crossover design. The 1st primary outcome in the trial (NCT 00364182) is analyzed as a continuous outcome. The treatment effect is estimated by comparing baseline (On-demand) level to the average of those receiving from both randomization period 1 and period 2, or comparing pooled data from both periods for each treatment, which does not appropriately address the crossover design.*

| | |
|---|---|
| **Measure Type** | Primary |
| **Measure Title** | Annualized Number of Bleeding Episodes |
| **Measure Description** | Annualized bleed rate (ABR) or number of bleeds per year derived for each participant for each treatment regimen by using the following formula: ABR = number of bleeds / (days on treatment regimen / 365.25) |
| **Time Frame** | Baseline up to Week 56 |
| **Safety Issue** | No |




**Reporting Groups**

| | Description |
|---|---|
| **BeneFIX OD1** | BeneFIX on-demand IV bolus infusion for 16 weeks (first intervention) |
| **BeneFIX 100 IU/kg** | BeneFIX 100 IU/kg IV bolus infusion QW for 16 weeks |
| **BeneFIX 50 IU/kg** | BeneFIX 50 IU/kg IV bolus infusion BW for 16 weeks |

**Measured Values**

| | BeneFIX OD1 | BeneFIX 100 IU/kg | BeneFIX 50 IU/kg |
|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **50** | **44** | **44** |
| **Annualized Number of Bleeding Episodes [units: episodes] Least Squares Mean ( 95% Confidence Interval )** | **35.1 ( 28.8 to 41.4 )** | **4.6 ( 2.1 to 7.2 )** | **2.6 ( -0.1 to 5.3 )** |

**Statistical Analysis 1 for Annualized Number of Bleeding Episodes**

| | |
|---|---|
| **Groups** [1] | BeneFIX OD1 vs. BeneFIX 100 IU/kg |
| **Method** [2] | ANOVA |
| **P Value** [3] | <0.0001 |
| **Mean Difference (Final Values)** [4] | -30.5 |
| **95% Confidence Interval** | ( -36.5 to -24.5 ) |

Example for question 38:

*Example:*

*The trial (NCT00383162) did not present results by period.*

**Measured Values**

| | Placebo | Sumatriptan-Naproxen Sodium |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | **133** | **136** |
| **Sustained Freedom From Migraine Pain Between 2-24 Hours Post-dose [units: Participants]** | **10** | **36** |

Example for question 39:

*Example 1: With Statistical analysis*

**Statistical Analysis 1 for Adherence With Treatment in the First Treatment Period**

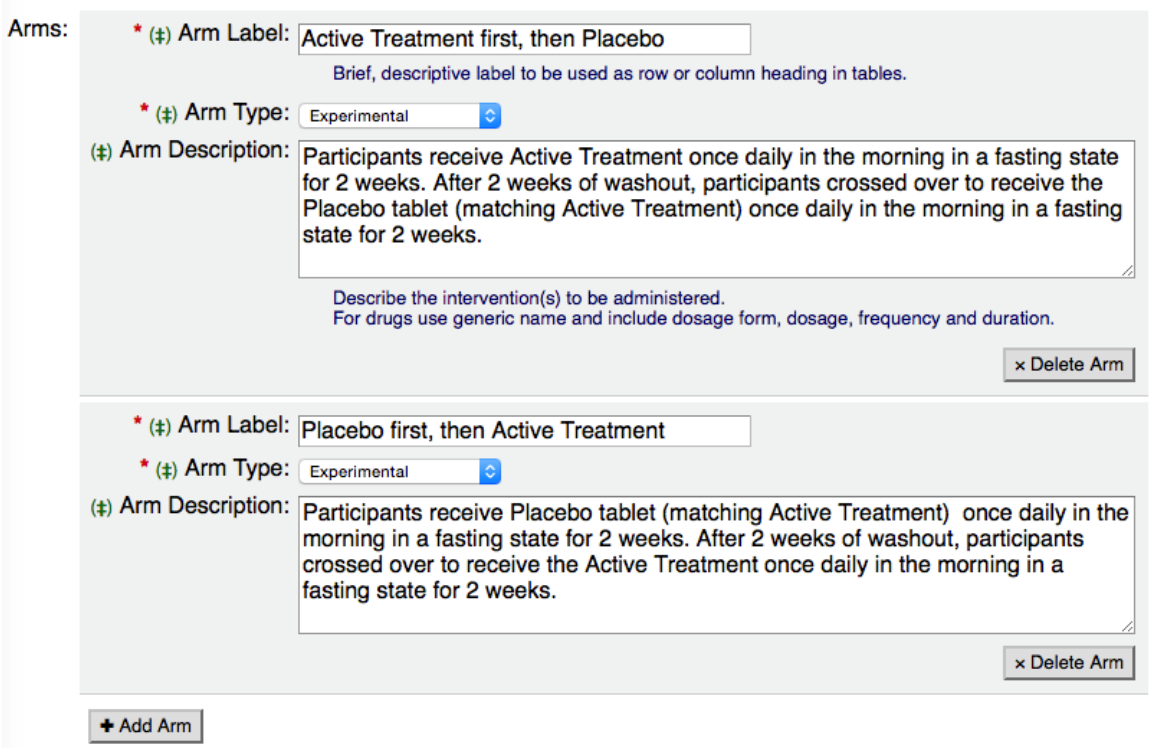
*Example 2: Without statistical analysis*

**No statistical analysis provided for Maximum Percent Fall in FEV1**

**Appendix 4. Illustration of registering 'Arms/Interventions' on ClincialTrials.gov system**

When registering 'Arms' information on ClinicalTrials.gov system, registrars are required to provide at least 'Arm Label' and 'Arm Type' information in order to register a certain arm. Additionally, there is an optional cell for 'Arm Description' for each arm section. An illustrative example of registering 'Arms' details on registration system was shown in Figure 17.

**Figure 17. Illustration for registering 'Arms' details on ClinicalTrials.gov system**




Then registrars register all interventions involved in the trial in a separate page in a format shown in Figure 18. Finally, assigned interventions are identified by checking the cross-reference table to link interventions with a certain arm (Figure 19). All checked

interventions would be listed in ‘Assigned Interventions’ columns corresponding to each specified arm.

**Figure 18. Illustration of registering ‘Interventions’ on ClinicalTrials.gov system**

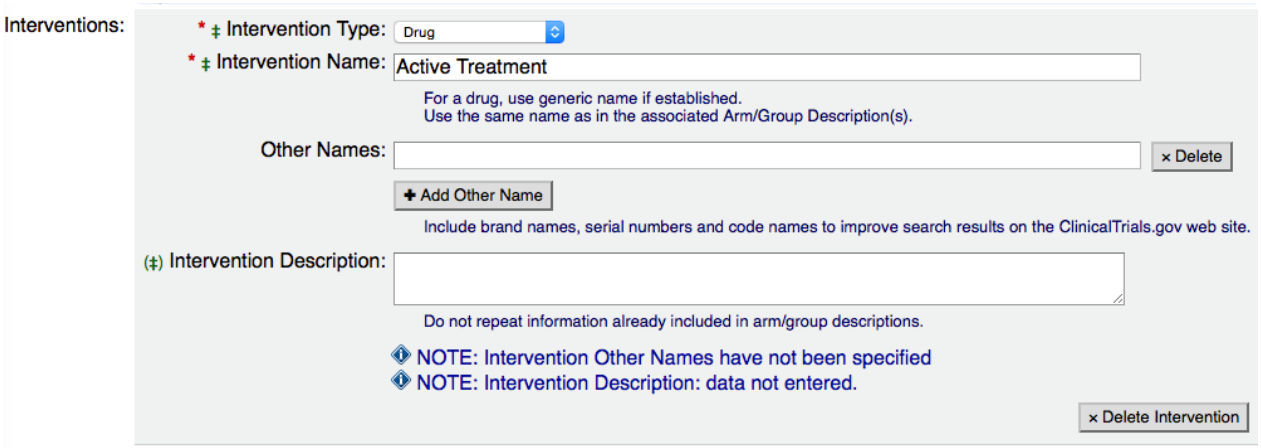
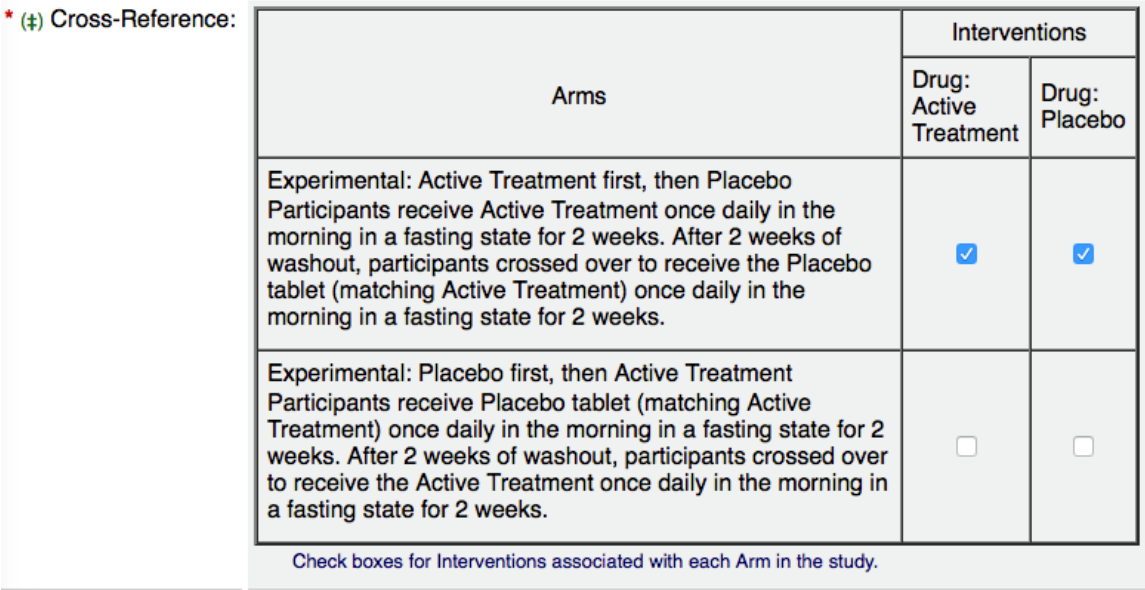



**Figure 19. Illustration checking arm/intervention ‘Cross-Reference’ table on ClinicalTrials.gov system**



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**CURRICULUM VITAE**


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## EDUCATION

**Master of Health Science (MHS)** May 2015
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health (JHBSPH), Baltimore, MD
**Concentration**: Clinical Trials and Evidence Synthesis
**Relevant Coursework**:

- Statistical related: Multilevel Statistical Models, Longitudinal Data Analysis, Causal Inference, Advanced Methods for Design & Analysis of Cohort Studies, Methods in Biostatistics I-IV, Statistical Computing
- Clinical trials and epidemiology related: Clinical Trials Management, Data Management in Clinical Trials, Epidemiologic Methods, Methodologic Challenges in Epidemiologic Research, Epidemiology of Aging, Eye Disease (Epi & Control),
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**Bachelor of Science in Pharmaceutical Science** Jul 2013
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## RESEARCH EXPERIENCE

**Research Assistant** May 2014 – Present
Center for Clinical Trials and Evidence Synthesis, Johns Hopkins Bloomberg School of Public Health

- Led an independent project in assessing the crossover trials registered on ClinicalTrials.gov: identified key issues in the current registration system and provided guidelines for ClinicalTrials.gov to improve the registration for crossover design trials
- Involved in systematic reviews led by Cochrane Eyes and Vision Groups, including screening, data extraction and quality assessment.

**Center Scholar** May 2014 – Present
Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health

- Conducted drug utilization research to examined the controlled substance utilization patterns;
- Analyzed IMS claims data with SAS programming

## TEACHING EXPERIENCE

**Teaching Assistant** Jun 2014 – Jan 2015
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
Assisted in teaching three graduate-level courses: led discussions, held office hours, attended instructors' meetings, graded assignments

- Course: Conduct and Design of Clinical Trials
- Course: Introduction to Clinical Trials
- Course: Pharmacoepidemiology Methods

## WORKING EXPERIENCE

**Sales Force Effectiveness (SFE) Analyst** 2012.10 – 2012.12
Baxter International Inc., Shanghai, China

- Maintained and administered company's sales force platform using Salesforce.com
- Analyzed SFE data to evaluate the sales representatives' performances
- Trained pharmaceutical sales representatives using SFE system

**SFDA Intern** 2012.8 – 2012.9
Division of Inspection, Shanghai Food and Drug Administration

- Reviewed inspection documents for drugs and devices
- Prepared profiles and assisted in random product checks

## POSTER/PRESENTATION

**Zeng, L**. Drye, L. Li, T. "Characterizing current registration of phase 3 crossover trials on ClinicalTrials.gov", Society for Clinical Trials (May 2015)

## PROFESSIONAL DEVELOPMENT

**Software:** R, SAS, STATA, Microsoft Office Suite, LaTeX, Tableau, SQL, REDCap
**Language:** English, Chinese, Japanese
**Membership:** Society for Clinical Trials (2014 – Present)