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Analysis of Two-Stage Seamless Adaptive Design – Application in Liver Disease Clinical Trials

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Outline

- General concept of adaptive design
- Two-stage seamless adaptive design
  - Types of two-sage seamless adaptive design
- Analysis of two-stage seamless adaptive design
- Typical questions from US FDA
- Case studies
  - HCV study
  - NASH study
- Concluding remarks
  - Recent FDA draft guidance on NASH

What is an adaptive design?

US FDA Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologics, 2010, 2018

An adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study

US FDA's definition

- Comments
  - It is not flexible because only prospective adaptations are allowed
  - It does not reflect real practice (e.g., protocol amendments)
  - It does not mention validity and integrity?
  - Interpretations vary from reviewer to reviewer
  - FDA encourages the sponsors consulting with reviewers when utilizing adaptive design
    - subjective
    - case-by-case means no standard

Adaptation

- An adaptation is defined as a change or modification made to a clinical trial before and during the conduct of the study.
- Examples include
  - Relax inclusion/exclusion criteria
  - Change study endpoints
  - Change hypotheses
  - Modify dose and treatment duration

  etc.

Types of adaptations

- Prospective adaptations
  - By design
  - Implemented by study protocol
- Concurrent adaptations
  - Changes made during the conduct of the study
  - Implemented by protocol amendments
- Retrospective adaptations
  - Changes made after the conduct of the study
  - Implemented by statistical analysis plan prior to database lock and/or data unblinding

Types of adaptive designs

- Adaptive randomization design
- Group sequential design
- Flexible sample size re-estimation design
- Drop-the-losers (pick-the-winner) design
- Adaptive dose-finding design
- Biomarker-adaptive design
- Adaptive treatment-switching design
- Adaptive-hypotheses design
- Adaptive seamless design
  - Two-stage phase I/II (or II/III) adaptive design
- Multiple adaptive design (any combinations of the above designs)

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Review

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Adaptive design methods in clinical trials – a review

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Abstract

In recent years, the use of adaptive design methods in clinical research and development based on accrued data has become very popular due to its flexibility and efficiency. Based on adaptations applied, adaptive designs can be classified into three categories: prospective, concurrent (ad hoc), and retrospective adaptive designs. An adaptive design allows modifications made to trial and/or statistical procedures of ongoing clinical trials. However, it is a concern that the actual patient population after the adaptations could deviate from the originally target patient population and consequently the overall type I error (to erroneously claim efficacy for an infective drug) rate may not be controlled. In addition, major adaptations of trial and/or statistical procedures of on-going trials may result in a totally different trial that is unable to address the scientific/medical questions the trial intends to answer. In this article, several commonly considered adaptive designs in clinical trials are reviewed. Impacts of ad hoc adaptations (protocol amendments), challenges in *by design* (prospective) adaptations, and obstacles of retrospective adaptations are described. Strategies for the use of adaptive design in clinical development of rare diseases are discussed. Some examples concerning the development of Velcade intended for multiple myeloma and non-Hodgkin's lymphoma are given. Practical issues that are commonly encountered when implementing adaptive design methods in clinical trials are also discussed.

Two-stage seamless adaptive design

- Combine two separate and independent trials (e.g., phase 1 and phase 2) into a single trial
- The single trial will then consist of two stages
  - Stage 1: learning (exploratory) phase
  - Stage 2: confirmatory phase
- Opportunity for adaptations based on accrued data at the end of stage 1 (i.e., learning or exploratory phase)

An example

- Two-stage phase 2/3 study
  - Stage 1: learning (exploratory) phase
    - e.g., dose finding
      - May use biomarker or surrogate endpoints
      - Drop-the-losers or pick the winner
  - Stage 2: confirmatory phase
    - e.g., efficacy confirmation
      - Based on study endpoints
      - Hypotheses-adaptive

Advantages

- Flexibility
  - Modifying the study protocol as it continues for identifying any signal, trend, or pattern of clinical benefit or harms
- Efficiency
  - Can reduce lead time between the learning phase and the confirmatory phase
- Opportunity for saving
  - Stopping trial early for safety and/or futility/efficacy
- Combined analysis
  - Data collected at the learning phase are combined with those data obtained at the confirmatory phase for final analysis

Limitations – FDA's concerns

- May introduce operational bias
  - Adaptations relate to dose, hypothesis and endpoint etc.
- May not be able to control the overall type I error rate
  - When study objectives/endpoints are different at different stages
- Statistical methods for combined analysis are not well established
  - Complexity depends upon the adaptations apply

Practical issues

- In practice, an adaptive seamless design may combine two separate (independent) trials with similar but different study objectives into a single trial, e.g.,
  - A phase 2 trial for dose selection and a phase 3 study for efficacy confirmation
- In some cases, the study endpoints considered at the two separate trials may be different, e.g.,
  - A biomarker or surrogate endpoint versus a regular clinical endpoint

Types of two-stage seamless adaptive designs

- Study objectives at different stages
  - **S**ame study objective
  - **D**ifferent study objective
- Study endpoints at different stages
  - **S**ame study endpoints
  - **D**ifferent study endpoints

Types of two-stage seamless adaptive designs

		Study endpoints at different stages	
		S	D
Study objectives at different stages	S	I=SS	II-SD
	D	III=DS	IV=DD

Analysis of two-stage adaptive design

- SS design
  - Similar to group sequential design
- SD design
  - Study endpoint at the first stage is predictive of the study endpoint at the second stage
- DS design
  - Consider testing two sets of hypotheses at different stages
- DD design
  - Study endpoint at the first stage is predictive of the study endpoint at the second stage
  - Consider testing two sets of hypotheses at different stages

Pharmaceutica
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Chow and Lin, Pharm Anal Acta 2015, 6:3
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Review Article Open Access

Analysis of Two-Stage Adaptive Seamless Trial Design

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Abstract

In the past decade, adaptive design methods in clinical research have attracted much attention because it offers the principal investigators (1) potential flexibility for identifying clinical benefit of a test treatment under investigation, but efficiency for speeding up the development process. One of the most commonly considered adaptive designs is probably a two-stage seamless (e.g., phase I/II or phase II/III) adaptive design. The two-stage seamless adaptive designs can be classified into four categories depending upon study objectives and study endpoints at different stages. These categories include (I) design with same study objectives and study endpoints at different stages, (II) designs with same study objectives but different study endpoints at different stages, (III) designs with different study objectives but same study endpoints at different stages, and (IV) designs with different study objectives and different study endpoints at different stages. In this article, an overview of statistical methods for analysis of these different types of two-stage designs is provided. In addition, a case study concerning the evaluation of a test treatment for treating hepatitis C infected patients utilizing type (IV) trial design is presented.

Typical questions from FDA

- How to perform power analysis for sample size calculation/allocation?
  - Provide detailed information regarding which statistical methods are used for sample size calculation/allocation if possible
- How to prevent operational biases after the review of accumulated data at end of Stage 1?
  - Provide a list of possible operational biases
  - Provide strategy for presenting operational biases if possible

Typical questions from FDA

- Provide detailed information regarding criteria for making decision at the end of Stage 1
  - Precision analysis versus power analysis
- How to control the overall type I error rate at a pre-specified level of significance?
  - Especially when the study objectives at different stages are different

Typical questions from FDA

- How to combine data collected from both stages for a valid final analysis?
  - Especially when the study objectives and study endpoints at different stages are different
- Is the use of O'Brien-Fleming stopping boundaries valid/feasible?
  - Is the overall type I error rate still controlled especially where there is a shift in patient population (e.g., due to protocol amendments)

Case study #1 – the HCV study

- Background
  - A sponsor was interested in developing a drug product for treatment of patients with hepatitis C virus (HCV) genotype 1 infection.
  - After consulted with FDA reviewers, the sponsor planned to conduct a phase II study for dose finding and a phase III study for efficacy confirmatory in order to fulfill with FDA's requirement for regulatory submission.
  - The sponsor was interested in shortening the development process
  - The sponsor decided to conduct a single trial with two-stage seamless adaptive trial design

Case study #1 – the HCV study

- Two-stage seamless adaptive design
  - Study objectives are similar but different
  - Study endpoints are different
- Study objectives
  - Dose selection (phase 2)
  - Efficacy confirmation (phase 3)
- Treatment
  - 5 treatments including 4 active treatments (doses) and one placebo
-

Case study #1 – the HCV study

- Study endpoints
  - Stage 1: early virologic response (EVR) at week 12
  - Stage 2: sustained virologic response (SVR) at 72 week (i.e., 24 weeks after 48 weeks of treatment)
- Two-stage phase 2/3 seamless adaptive design
  - It is a DD design

Adaptations considered

- Two planned interim analyses
  - The first interim analysis will be performed when all Stage 1 subjects have completed study Week 12.
  - The second interim analysis will be conducted when all Stage 2 subjects have completed Week 12 of the study and about 75% of Stage 1 subjects have completed Stage 1 treatment.
  - The O'Brien-Fleming type of boundaries are applied.

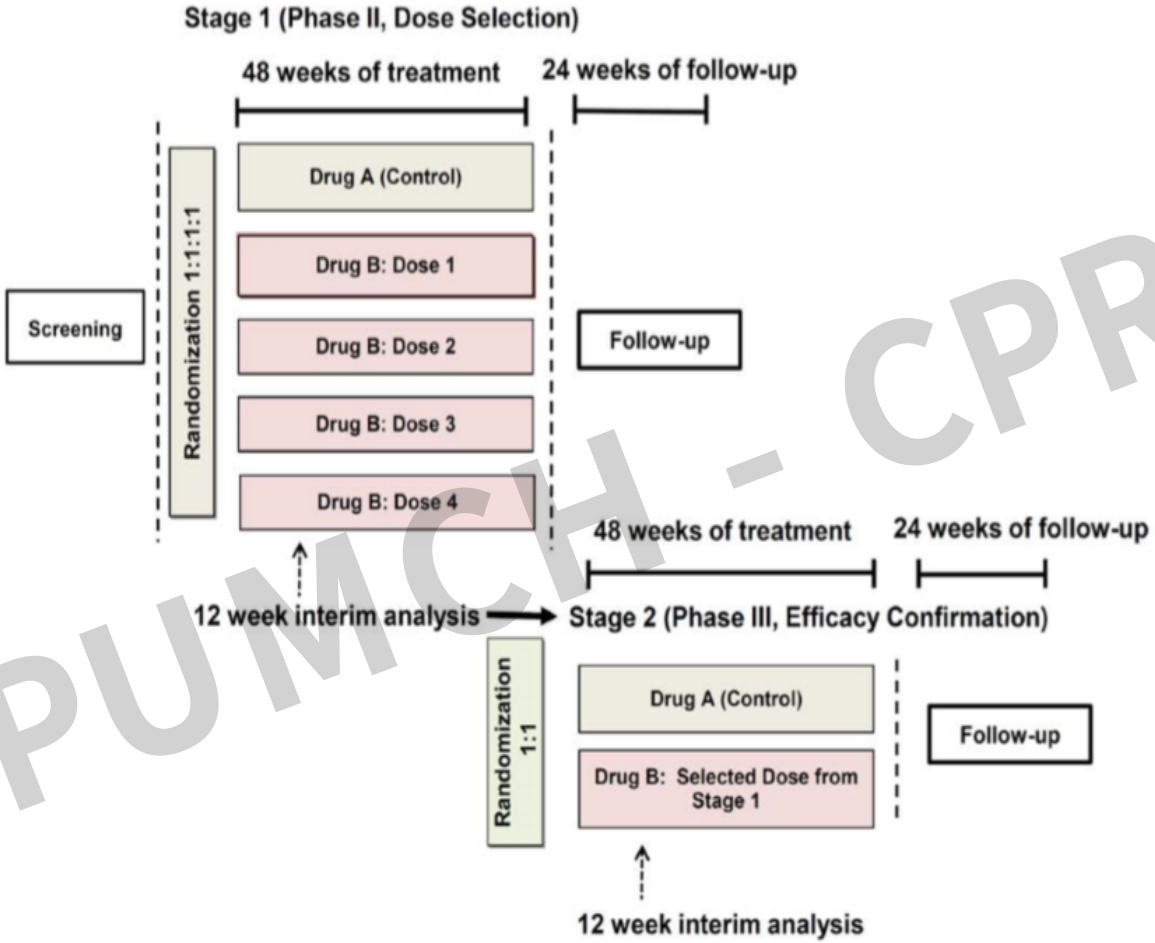


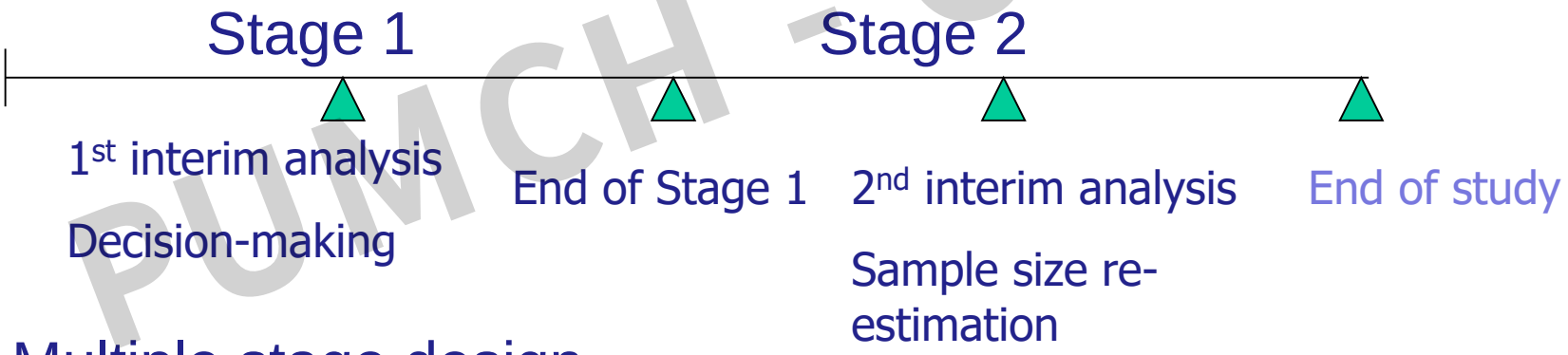
Figure 1: A diagram of 4-stage transitional seamless trial design.

Criteria for dose selection at Stage 1

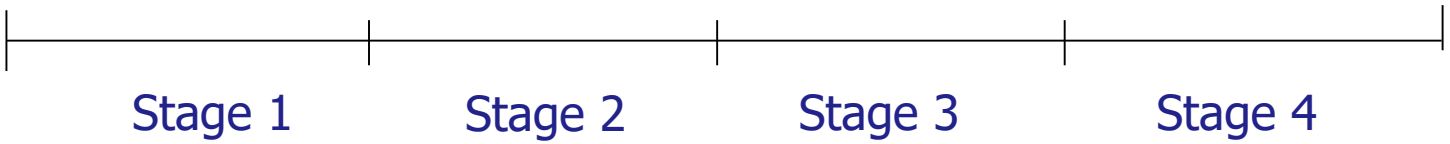
- Dose selection is performed based on the precision analysis.
  - Based on EVR, the dose with highest confidence level for achieving statistical difference (i.e., the observed difference is not by chance alone) as compared to the control arm is selected.

Convert the two-stage design into multiple-stage design

– Two-stage seamless adaptive design



– Multiple stage design



Consider test two sets of hypotheses

- Notations
  - $E_{i,j}$: treatment effect of the *i*th dose group at the *j*th stage based on surrogate endpoint
  - $\psi_{i,j}$: treatment effect of the *i*th dose group at the *j*th stage based on regular clinical endpoint

    i =1,…, k (dose group)

    j =1,2 (stage)

Test two sets hypotheses under the 4-stage design

- This two-stage seamless design can then be viewed as a 4-stage design
- Hypotheses of interest

$$H_{0,1}: \theta_{i,1} \leq 0, i = 1, \ldots, k$$

$$H_{0,2}: \psi_{i,2} \leq 0, i = 1, \ldots, k$$

Statistical tests under the 4-stage design

- Testing procedure
  - **Stage 1**
    - If $\max \hat{\theta}_{i,1} \le c_1$, then stop the trial.
    - If $\max \hat{\theta}_{i,1} > c_1$, then treatment E_{i^*} will proceed to Stage 2, where $i^* = \arg\max_{1 \le i \le k} \hat{\theta}_{i,1}$
  - **Stage 2**
    - If $T_{2,1} = \frac{n_1}{n_1 + n_2} \hat{\theta}_{i^*,1} + \frac{n_2}{n_1 + n_2} \hat{\theta}_{i^*,2} \le c_{2,1}$, then stop the trial.
    - If $T_{2,1} > c_{2,1}$ but $\psi_{i^*,1} \le c_{2,2}$ then move to Stage 3.

Statistical tests under the 4-stage design

– **Stage 3**

- If $T_{3,2} = \frac{n_1}{n_1 + n_2}\hat{\psi}_{i^*,1} + \frac{n_2}{n_1 + n_2}\hat{\psi}_{i^*,2} > c_3$,

  stop the trial; otherwise move to Stage 4.

– **Stage 4**

- If $T_{4,2} = \frac{n_1}{n_1 + n_2 + n_3}T_{3,2} + \frac{n_2}{n_1 + n_2 + n_3}\hat{\psi}_{i^*,2} > c_4$

  reject $H_{0,2}$.

Challenges from the FDA

- Controlling type I error rate
  - Chow, S.C. and Lin, M. (2015). Analysis of two-stage adaptive seamless trial design. *Pharmaceutica Analytica Acta*, 6:3 http://dx.doi.org/10.4172/2153-2435.1000341
- Sample size calculation/allocation
  - Clinical trial simulation
  - Allocation ratio based on sample sizes of individual studies
- Criteria for dose selection
  - Precision analysis
  - Conditional power
  - Predictive probability of success
  - Probability of being the best dose or treatment

Criteria for Dose-Finding in Two-stage Seamless Adaptive Design

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Abstract

In pharmaceutical/clinical development, two-stage seamless adaptive designs are commonly considered. Such designs include a two-stage phase I/II or phase II/III adaptive trial that combines one phase IIb study for dose finding or treatment selection and one phase III study for efficacy confirmation into a single study. At the end of stage 1, promising dose(s) will be selected based on pre-specified selection criteria. In practice, since there is little power with limited subjects available at interim, commonly considered selection criteria for critical decision-making include (i) conditional power, (ii) precision analysis, (iii) predictive probability of success, and (iv) probability of being the best dose or treatment. The selected promising dose(s) will then proceed to the next stage for efficacy confirmation. In this article, we introduce, compare, and evaluate these criteria. Simulation studies and a numeric example are given to illustrate those criteria. Besides, we attempt to address some concerns for two-stage seamless adaptive clinical trial.

Case study #2 – the NASH study

- Background
  - A sponsor was interested in developing a drug product for treatment of patients with precirrhotic Non-Alcoholic Steatohepatitis (NASH).
  - For development of drug products treating patients with NASH, the following trials are necessarily conducted
    - Early phase trials/proof-of-concept
    - Phase 2 dose ranging
    - Phase 3 trials
    - Phase 4 post-marketing study

Case study #2 – the NASH study

- Some facts on NASH
  - NAFLD was the most common cause of cirrhosis
  - NAFLD is predictive of mortality of NASH in the presence of significant fibrosis
  - There are no validated surrogate endpoint to clinical outcomes
  - There is currently no approved drug therapy for NASH
  - The development of drug therapy is considered a public health priority

Case study #2 – the NASH study

- Concerns
  - The sponsor is not sure what endpoints should be used at different phases of clinical trials in the development of the drug product for NASH
  - The sponsor is not sure whether to conduct separate trials (e.g., a dose ranging trial and an efficacy confirmatory study) or a two-stage adaptive trial that combines the two studies into a single trial.

Case study #2 – the NASH study

- Why adaptive design?
  - Uncertainties about progression disease
  - Limited number of patients willing to have multiple liver biopsies
  - Lack of validated surrogate endpoint
  - The need for long-term exposure to assess an impact in outcome
- Two-stage seamless adaptive design
  - Flexibility and efficiency
  - Validity and integrity
  - Shorten the development process

TABLE 2. RELATIVE MERITS AND LIMITATION OF TWO-STAGE ADAPTIVE DESIGN IN NASH

Characteristic	Two Independent Trials	Two-Stage Adaptive Design
Power	90% 90% (81%)	90%
Sample size	N=N1+N2	N < *N1+N2**
Operational bias	Less	Moderate to severe
Data analysis	By study analysis	Combined analysis
Efficiency	6 to 12 months lead time between studies	Reduced lead time between trials
Flexibility/long-term follow-up	New study design based on previous data. New patients are enrolled	Adaptations based on IA, e.g., stop one or more study arms/randomize more patients. Continue follow-up
Regulatory aspects	Standard practice	Requires buy-in by global authorities prior to initiation
Statistical perspective	Valid statistical methods are well established	Evolving statistical methods
Operational complexity	Low	High

*Depends on adaptations; N is total number of subjects for both studies; N1 is the sample size for trial 1; N2 is the sample size for trial 2.

Case study #2 – the NASH study

- Study design
  - The sponsor decided to consider the following adaptive design for the development of the drug product for NASH
    - Proof-of-concept/dose ranging adaptive trial design
    - Phase 3/4 adaptive trial design
    - Phase 2/3/4 adaptive design
- Study endpoints and target patient populations at different phases

TABLE 1. ENDPOINTS AND POPULATION IN CLINICAL TRIALS IN NASH

Phase	Primary Endpoint	Target Population
Early phase trials/ Proof-of-concept	Endpoints should be based on mechanism of drug. Reduction in liver fat with a sustained improvement in transaminases; Improvement in biomarkers of liver inflammation, apoptosis and/or fibrosis. Consider using improvement in NAS (ballooning and inflammation) and/or fibrosis.	Ideal to enroll patients with biopsy-proven NASH but acceptable to enroll patients at high risk for NASH (i.e., evidence of fatty liver, two components of the metabolic syndrome, evidence of liver stiffness by imaging).
Dose ranging/phase 2	Resolution of NASH without worsening of fibrosis; alternatively, improvement in disease activity (NAS)/improvement in ballooning/ inflammation without worsening of fibrosis.	Biopsy-proven NASH and NAS $\geq$4. Include patients with NASH and liver fibrosis. Include a sufficient number of patients with NASH and fibrosis stage 2/3 to inform phase 3.
Trials to support a marketing application: phase 3	Resolution of steatohepatitis and no worsening of fibrosis. Improvement in fibrosis with no worsening of steatohepatitis. A co-primary endpoint of the above or depending on the mode of action, either one or the other can be used.	Patients with biopsy-confirmed NASH with moderate/advanced fibrosis (F2/F3).
Trials to support a marketing application: phase 4 (postmarketing part)	Clinical outcome trial underway by the time of submission: Composite endpoint: histopathologic progression to cirrhosis; MELD score change by $>$2 points or MELD increase to $>$15 in population enrolled with MELD $\leq$13; death; transplant; Cirrhosis decompensation events:	Patients with biopsy-confirmed NASH with moderate/advanced fibrosis (F2/F3).

Abbreviation: MELD, model for end-stage liver disease.

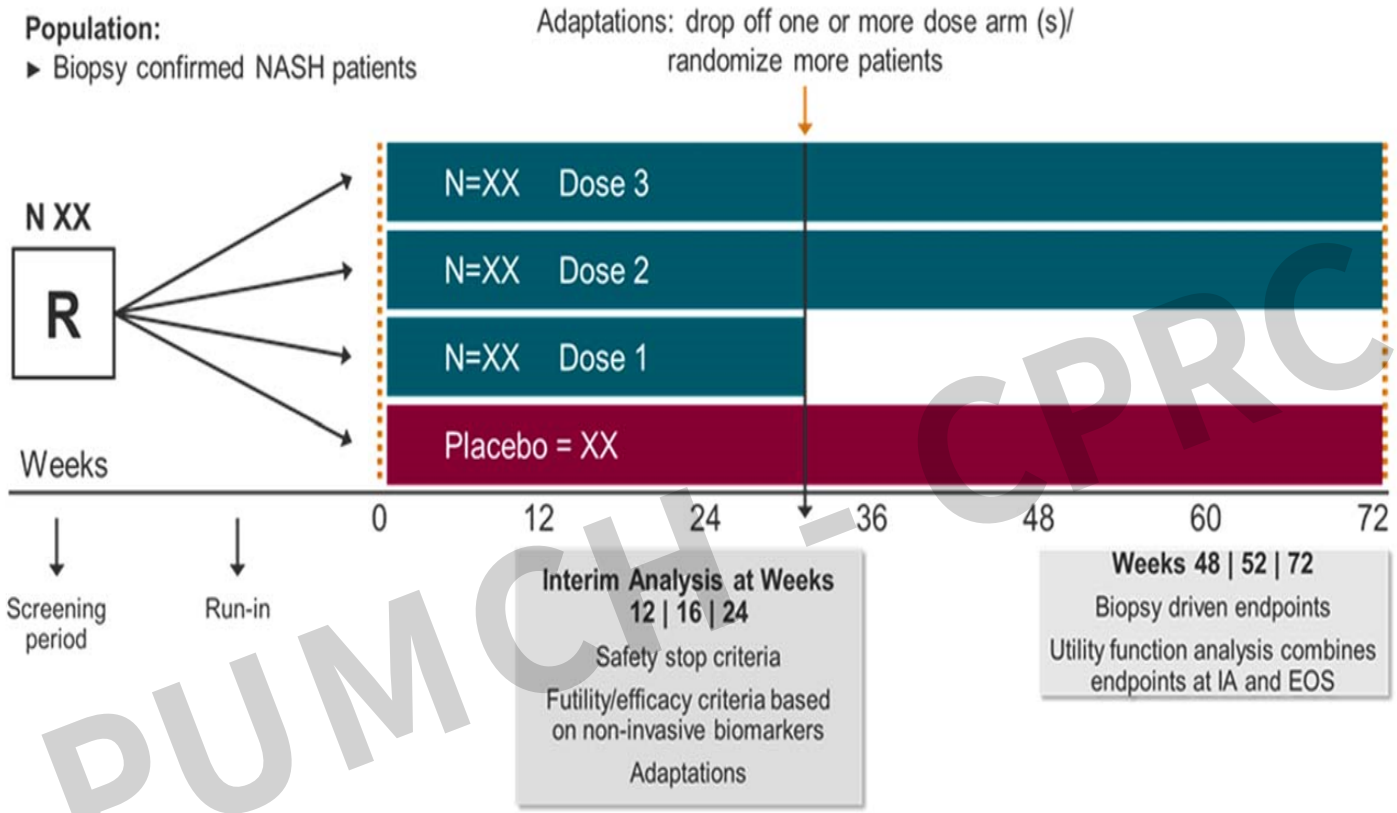

FIG. 1. Proof-of-concept/dose-ranging adaptive design trial. A single proof-of-concept dose-finding study seamless adaptive trial design can enroll patients with biopsy-confirmed NASH and allow adaptations, rolling over those patients on the most promising doses. The evaluation of changes in liver fat and other noninvasive biomarkers of liver function, inflammation, and fibrosis may help in decision making during the IA after a prespecified period. At this point, efficacy and futility analysis allows adaptations (i.e., drop-off study arm/s, randomize more patients, stop the study if a safety concern arises). The continuous follow-up allows the evaluation of changes in liver histology in the selected dose/s. Abbreviations: EOS, end of study; IA, interim analysis; N, number of subjects per study arm; R, randomized patients.

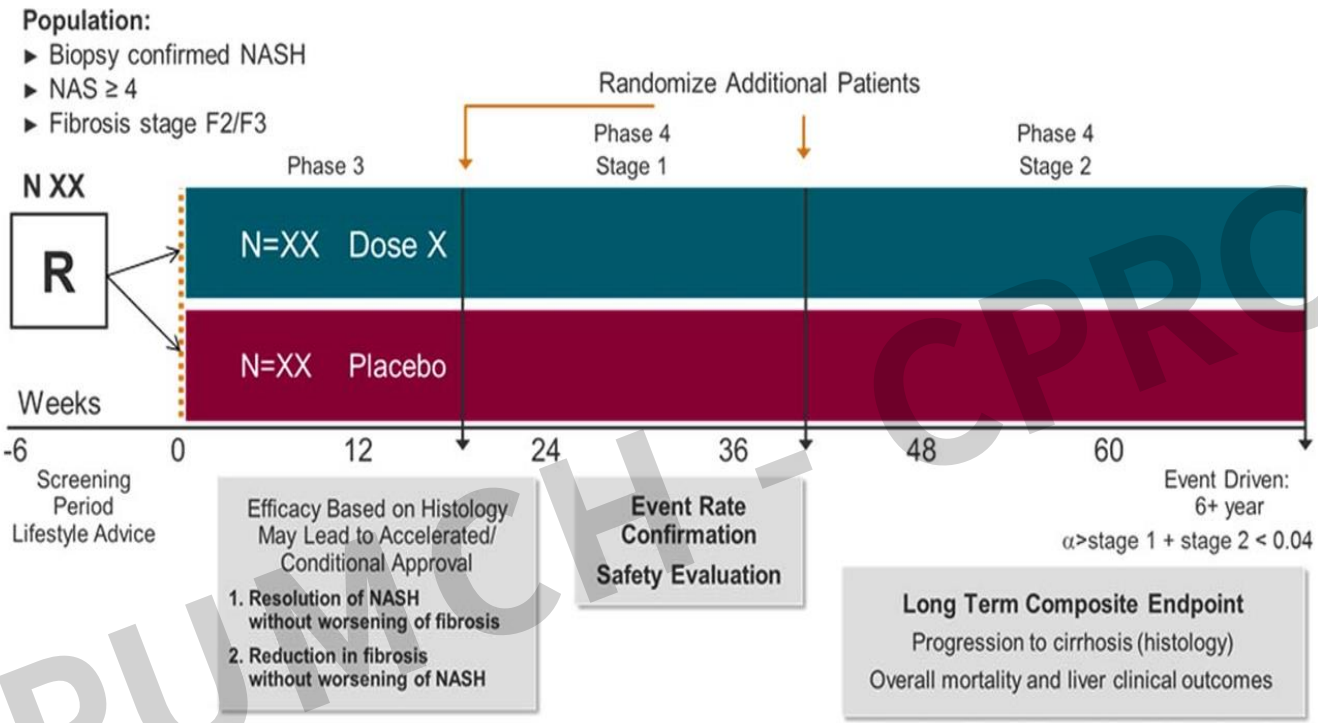

FIG. 2. Phase 3/4 adaptive design. A single seamless adaptive trial design allows for continuous exposure and long-term follow-up. A therapeutic index (or utility) function can be adopted to link all NASH endpoints at different stages. Furthermore, different prespecified weights can be allocated in the function. Endpoints at the interim analysis are: i) resolution of NASH by histology without worsening of fibrosis and/or ii) improvement in fibrosis without worsening of NASH. If positive, a long-term follow-up to confirm efficacy in reduction in clinical outcome is mandatory. It is important to ensure type 1 error control. At present, because marketing authorization is based on a surrogate endpoint that is "reasonably likely to predict benefit on morbidity or mortality," based on epidemiologic data but not "surrogates that are validated by definitive studies," a smaller alpha is allocated to the first test compared to the second one (e.g., 0.01 and 0.04, respectively). Abbreviations: N, number of subjects per study arm; R, randomized patients.

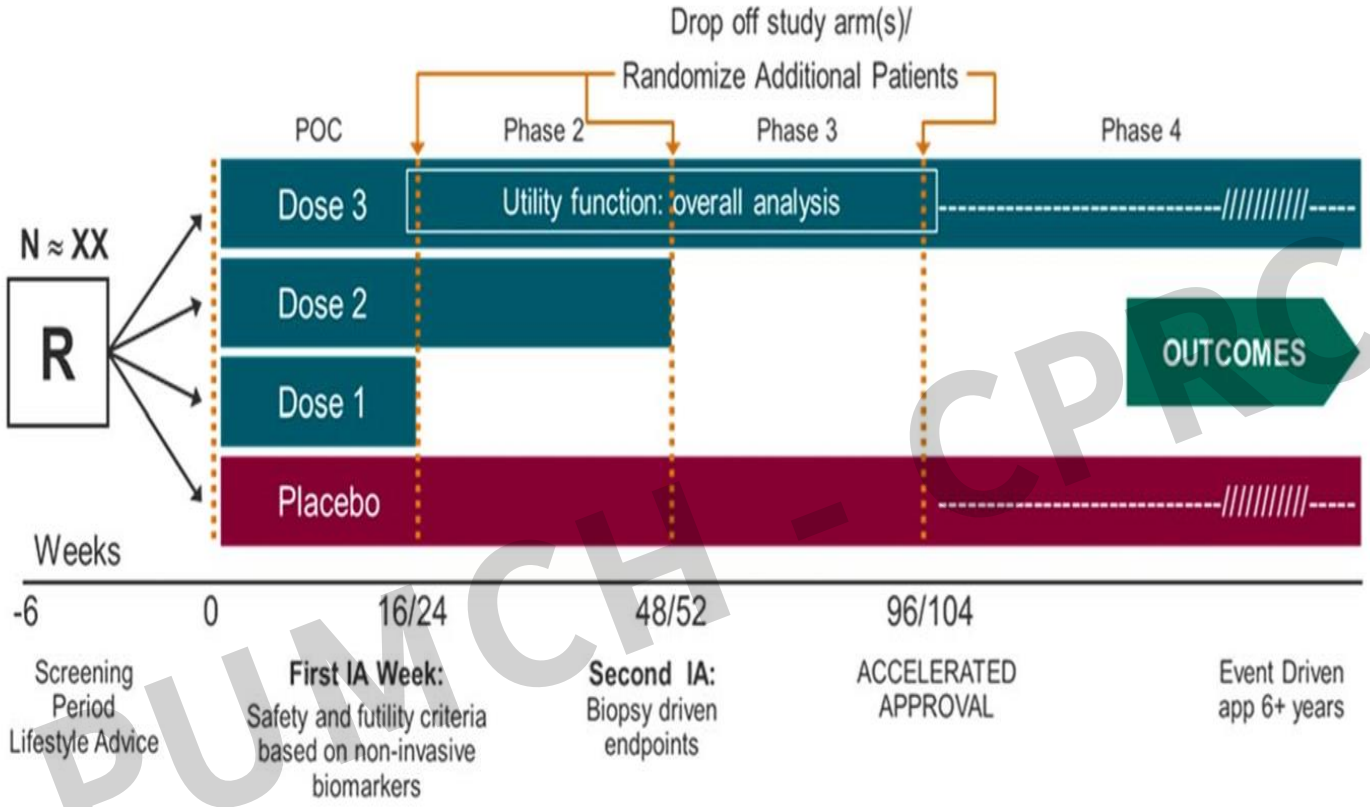

FIG. 3. Phase 2/3/4 adaptive design. A single seamless 2/3/4 adaptive trial design allows adaptations, continuous exposure, and long-term follow-up. Endpoints Ad interim analysis are reduction of at least 2 points in NAS, resolution of NASH by histology without worsening of fibrosis, and/or improvement in fibrosis without worsening of NASH. One (the most promising dose) or two doses may continue to the next phase. A postmarketing phase 4 with demonstration of improvement in clinical outcomes will lead to final marketing authorization. Because only one trial would lead to approval, a very small overall alpha (i.e., <0.001) is recommended to ensure proper control of a type I error. Abbreviations: IA, interim analysis; N, number of subjects per study arm; R, randomized patients.

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Clinical Endpoints and Adaptive Clinical Trials in Precirrhotic Nonalcoholic Steatohepatitis: Facilitating Development Approaches for an Emerging Epidemic

Claudia Filozof,[1] Shein-Chung Chow,[2] Lara Dimick-Santos,[3] Yeh-Fong Chen,[3] Richard N. Williams,[4] Barry J. Goldstein,[4] and Arun Sanyal[5]

Due to the increasing prevalence of nonalcoholic steatohepatitis (NASH) and its associated health burden, there is a high need to develop therapeutic strategies for patients with this disease. Unfortunately, its long and asymptomatic natural history, the uncertainties about disease progression, the fact that most patients are undiagnosed, and the requirement for sequential liver biopsies create substantial challenges for clinical development. Adaptive design methods are increasingly used in clinical research as they provide the flexibility and efficiency for identifying potential signals of clinical benefit of the test treatment under investigation and make prompt preplanned adaptations without undermining the validity or integrity of the trial. Given the high unmet medical need and the lack of validated surrogate endpoints in NASH, the use of adaptive design methods appears reasonable. Furthermore, due to the limited number of patients willing to have multiple liver biopsies and the need for long-term exposure to assess an impact in outcomes, a continuous seamless adaptive design may reduce the overall sample size while allowing patients to continue after each one of the phases. Here, we review strategic frameworks that include potential surrogate endpoints as well as statistical and logistical approaches that could be considered for applying adaptive designs to clinical trials in NASH with the goal of facilitating drug development for this growing medical need. (*Hepatology Communications* 2017; 00:000-000)

FDA's perspectives

- General consideration
  - Specify criteria that establish a diagnosis of cirrhosis
    - E.g., a diagnosis of cirrhosis should be supported by histology such as a NASH Clinical Research Network (CRN) fibrosis score of 4
  - Stratified randomization
    - E.g., patients with type 2 diabetes mellitus or patients with NASH-cirrhosis who are treated with Vitamin E or pioglitazone
  - Sufficient duration and adequate sample size
  - FDA encourages the use of biochemical or imaging non-invasive biomarkers that can replace liver biopsies
  - Establishment of expert committee to adjudicate cases for safety

Remarks

- Since study endpoints and target populations are very different at different phases of clinical development for NASH, this leads to the development of therapeutic index for an overall assessment of treatment effect
  - Therapeutic index is developed based on a set of evaluation criteria at different phases of clinical development

Development of therapeutic index for NASH

Let $y = \{y_1, y_2, \ldots, y_m\}$ be the endpoints of interest. Each of these endpoints, y_i is a function of criteria $y_i(x),\ x \in X$, where X is a space of criteria. Therapeutic index is defined as

$$U_{sk} = \sum_{j=1}^{m} w_{skj} = \sum_{j=1}^{m} w(y_{skj}), k = 1, .., K; s = 1, .., S,$$

where U_{sk} denotes the kth endpoint derived from the therapeutic index at the sth stage of the multiple-stage adaptive design and $w_{skj}, j = 1, \ldots, m; k = 1, \ldots, K$ are pre-specified weights.

Development of therapeutic index for NASH

As an example,

if $K = 1, U_{sk} = U_s$, which reduces to a composite index such as NAS ≥4 and/or F2/F3 (fibrosis stage 2 and fibrosis stage 3) at the sth stage.

When K =2, the therapeutic index function for endpoints suggest a co-primary, i.e., $U_{s1}\ and\ U_{s2}$ at the sth stage.

Concluding remarks

- Flexibility and efficiency are usually achieved at the risk of quality, validity, and integrity
  - More flexible (adaptations) means more problematic
- Most recently, FDA suggests the use of phase 2/3/4 adaptive design for evaluation of drug products for treatment of patients with NASH
  - Statistical methodologies are not fully developed
- Recent FDA draft guidance on NASH
  - Post more questions than answers
- That was then, this is now
  - Investigator's wish list

FDA guidance on NASH

- Standard of care considerations for clinical trials of drugs intended to treat NASH
  - Standard of care and background therapy should be stable for at least 3 months prior to enrollment
- Pre-cirrhotic NASH with liver fibrosis: developing drugs for treatment
  - Prevent progression to cirrhosis and its complications
  - Reduce the need for liver transplantation and improve survival
- Compensated cirrhosis in NASH: developing drugs for treatment
  - There are currently no FDA-approved drugs for compensated NASH cirrhosis

Investigator's wish list

- That was then
  - Select an appropriate study design from a group of candidate designs
  - The selected study design is able to address the study objectives of a given clinical study
  - Not flexible and usually with limitations
- This is now
  - Based on investigator's wish list, come up with a flexible adaptive study design
  - The selected study design is able to address the study objectives of a given clinical study
  - More flexible means more problematic
  - **Clinician should be in the driver seat**

Thank You for Your Attention!

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