Adaptive Clinical Trial Design: An Overview and Potential Applications in Dermatology

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The challenges of drug development, including increasing costs, late-stage drug failures, and the decline in the number of drugs being approved by the US Food and Drug Administration over time, have generated interest in adaptive study designs that have the potential to address these problems. Adaptive trial designs use interim data analysis to amend trials, and have been recognized for more than a decade as a way to increase trial efficiency, partly by the increased probability of demonstrating a drug effect if one exists. In this article, we define adaptive trials; give examples of the most common types; highlight the pros, cons, and ethical considerations of these designs; and illustrate how these tools can be applied to drug development in dermatology.

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INTRODUCTION

Despite substantial progress in the treatment of dermatologic diseases with the advent of biologic treatments for psoriasis and the use of immunomodulatory therapies for a wide array of autoimmune skin conditions, there remains much uncertainty regarding the effectiveness of treatments, as well as which treatments should be used as the first line. Furthermore, development of therapeutic strategies for certain diseases, such as bullous disorders and cutaneous vasculitis, remains challenging. Because the clinical development of novel therapeutics and the testing of existing therapeutics is expensive and time consuming, there is interest in using new study designs and statistical methods that have the potential to increase the efficiency of drug development (Chow, 2014).

Specifically, pharmaceutical innovation is increasingly risky and costly. Because of late-stage drug failures and rising costs of confirmatory trials, costs of bringing new drugs to the market are high, and have led to decreased industry productivity as a whole (Booth and Zemmel, 2004). Traditional clinical trials utilize prespecified elements, including primary endpoint, clinically meaningful treatment difference, and measures of variability among study participants to design the study. Data are then collected and analyses are performed. Ultimately, the success and the statistical power of these trials depend on the accuracy of the original clinical estimates, which are often inaccurate. To address the inefficiency in the traditional clinical trial, adaptive trial designs have been developed.

Adaptive clinical trial designs, those that use interim data analysis to amend trials, have been recognized for more than a decade as a way to increase trial efficiency by means of shorter duration, fewer participants, and, in some adaptive designs, increased probability of demonstrating an effect of the drug if one exists. They also help to address the uncertainty about the choices made during trial planning, such as subject variability and meaningful treatment effect. Examples of modifications or adaptations to increase efficiency and the probability of a successful trial include adjustments to sample size, changes in allocation to treatment arms, addition or deletion of treatment arms, adjustment of statistical hypotheses (e.g., noninferiority or superiority), and combination of trial treatment phases. However, although these adaptations may result in more efficient trials, they can raise concerns about treatment safety. Adaptations often result in the collection of fewer observations than traditional trials, which may reduce the ability of the trial to identify adverse events and other safety issues.

There are a number of requirements for successful implementation of adaptive designs; they require an infrastructure that facilitates rapid communication across trial sites and with the data monitoring committee, a flexible drug supply process, drug responses to be rapidly observable, and more upfront statistical work, requiring efficient design and fast computing (Orloff et al., 2009). Because adaptive trials are less well understood than traditional designs, simulation studies are often required to test the validity and robustness of the trial design, which is not necessary for traditionally designed trials (Burton et al., 2006).

To date, adaptive designs have mostly been studied in the statistical, pharmaceutical, and regulatory fields. Clinicians, especially in the fields of oncology and cardiology, have begun to implement these designs, and it is likely that these designs will expand to other medical fields, as well (Barker et al., 2009; Bhatt et al., 2013).

In this article, we define adaptive designs; give examples of types of adaptive designs; highlight the pros, cons, and ethical considerations of these designs; and illustrate how

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Abbreviation: FDA, US Food and Drug Administration

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these tools can be applied to exploratory and confirmatory drug development using relevant case examples from dermatology. Our goal is not to prove that adaptive designs are the best alternative to traditional designs, but rather to encourage those running trials to explore these methodologies with the hope of adding value to clinical trial efficiency and efficacy.

DEFINITION

Although there is often confusion as to what is meant by adaptive design, recent publications have helped to clearly define this term. In 2005, a working group sponsored by the Pharmaceutical Research and Manufacturers of America defined an adaptive design as "a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial," stressing that the modifications should be prespecified and by design. The working group emphasized that adaptive designs are not a solution for inadequate planning, but are meant to enhance study efficiency (Gallo et al., 2006).

In 2010, the US Food and Drug Administration (FDA) released a draft guidance, "Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics," which defines adaptive designs as studies that "include 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" (FDA Draft Guidance, 2010). "Prospective" in this definition means that possible modifications are specified before the data are examined in an unblinded manner. This feature differentiates the FDA definition from the Pharmaceutical Research and Manufacturers of America one. The document further classifies adaptive trials into two categories, those that are "well-understood" and those that are "less well-understood." Well-understood designs are those whose properties have been well characterized using statistical methods that are accepted, especially with regard to controlling type I error. Briefly, type I error is the probability of incorrect rejection of a true null hypothesis, also known as a "false positive." Those designs described as less well-understood have not been fully evaluated, and their merits and associated statistical methods are less accepted or even known, but the assumption is that there is a greater risk of type I error in these study designs. This draft guidance was intended to assist trialists in designing adaptive studies that would meet the FDA's standards for approval (US Food and Drug Administration: Draft Guidance for Industry, 2010).

It is important to differentiate between the aforementioned definitions of adaptive designs and what others have referred to as "flexible designs" (Chow and Chang, 2007). The difference, described by Brannath et al. (2007), highlights that adaptive designs are not "flexible," in that how the interim data determine the design of the second part of the trial is completely prespecified ahead of the trial initiation.

Several researchers have criticized the above definitions for being too rigid, because it is very difficult for trialists to identify and propose all modifications prospectively (Chow, 2014). Chow broadens the range of adaptations by defining adaptive designs as those that "allow for adaptations in trial procedures and/or statistical procedures after initiation of the trial without undermining the validity and integrity of the trial," which allows for prospective, concurrent, and retrospective adaptations (Chow et al., 2005).

For the purposes of adaptive designs in dermatology, we will adopt the Chow definition as outlined above, as this definition reflects current practice of adaptive designs, with increasingly sound statistical methods to uphold the validity of such trials.

EXAMPLES OF ADAPTIVE TRIAL DESIGNS

Currently, adaptive design methods are accepted in exploratory stages of clinical trials, because their results must be validated in subsequent studies that meet FDA requirements (Coffey and Kairalla, 2008; US Food and Drug Administration: Draft Guidance for Industry, 2010). This allows for designs that give less emphasis to the control of type I error. In early development processes, adaptive designs can allow researchers to learn and optimize based on information related to dosing, exposure, and differential participant response.

There are numerous examples of adaptive designs; for the sake of brevity, we highlight those that may have particular use in dermatologic trials.

Adaptive group sequential design

Adaptive group sequential designs are essentially classical group sequential designs in which the sample size is not fixed and accumulating data are periodically analyzed with the intention of stopping the trial when a prespecified stopping criterion is met, with options of additional adaptations (e.g., sample size re-estimation, modification of treatment arms, dose selection, change of study endpoints, or modification of use or duration of treatment). In a group sequential design, the trial starts with a large upfront sample size, but provides the opportunity for early termination if accruing data suggest that the large sample is not needed (Jennison and Turnbull, 2000). Furthermore, this methodology allows for the discontinuation of the study if it is unlikely to meet its primary objective. This is called "futility," and may save resources and avoid the exposure of participants to a treatment of limited value. The FDA considers group sequential designs to be "well-understood," given that statistical methods for controlling the overall type I error rate are well established. However, the optional additional adaptations listed above may challenge the validity and statistical integrity of the trial by increasing type I error, and are therefore, deemed "less well-understood" by the FDA. There is also a concern that if a trial is stopped early because the stopping criterion is met, there is ultimately a smaller sample studied for a shorter duration, which may result in lost data relating to safety.

Adaptive sample size re-estimation design

Adaptive sample size re-estimation allows for adjustment of the sample size based on analyses of interim data. In general, sample size is determined before the trial formally starts based on the estimate of lowest clinically meaningful effect size between the treatment and control groups as well as an estimate of the variance between participants (Proschan, 2009). Incorrect initial parameters may lead to underpowered designs (Chow and Chang, 2011). Thus, it is of interest to