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Clinical trials in dermatology

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ABSTRACT

Clinical trials are the backbone of modern day medicine. Randomized, double-blinded, placebo-controlled studies are critical for advancement in medicine and dermatology. Skin conditions such as psoriasis and atopic dermatitis are among the most common health problems in the United States. Clinical trials can provide treatments that not only offer objective improvements in clinical disease status but also subjective improvements in the quality of life of patients who are afflicted with the disease. In this article, we discuss the processes and resources of a clinical trials unit and the challenges that can be encountered during the study process. It is critical to engage in clinical trials to treat patients most effectively with new and innovative therapies that are rooted in trial-validated, evidence-based medicine.

Introduction

The history of clinical research has evolved over centuries, between continents, and among disciplines into the modern era of clinical trials. The first recorded trial can be found in biblical writings between 605 and 562 BC. Records document an official order by King Nebuchadnezzar, a military leader in Babylon, that instructs people to eat a diet of meat and wine only, which he believed would keep them physically fit and healthy (Collier, 2009). However, a group of young men rebelled against the order and the king allowed them to consume vegetables and water instead. After 10 days, those with the vegetarian diet appeared better nourished than those who consumed the meat and wine diet (Collier, 2009). Despite its simplicity, this record of the first trial shows how experimentation has guided decisions, which in turn has had a broader impact on the overall public health (Bhatt, 2010; Collier, 2009).

Dr. James Lind is often credited with conducting the first clinical trial in modern times (Bhatt, 2010; Collier, 2009). Although the study was not perfect, he implemented the first control group within his study and found that adding citrus fruit to the diets of sailors could prevent scurvy (Bartholomew, 2002). By 1863, another element of modern clinical trial protocols, the placebo, was added to research studies (de Craen et al., 1999). In the1900s, more advanced concepts such as randomization and treatment blinding were introduced and utilized in research studies (Bhatt, 2010).

As the nature of clinical trials evolved, the protection of human study subjects also increased. Before the 20th century, ethical principles for the care of patients were rooted in the ancient Hippocratic Oath but not strictly adhered to and efforts to protect human subjects from harm or mistreatment were often reactionary rather than anticipatory. This issue was addressed with the creation of the Nuremberg Code and The Declaration of Helsinki, which outlined global rules of conduct for human experimentation. The United States also implemented its own laws and regulatory organizations to govern clinical trial research; however, many years, legislative acts, and unfortunate deaths passed before the U.S. Food and Drug Administration (FDA) in its current form was established to strictly regulate all stages of drug development, manufacturing, and marketing (Borchers et al., 2007).

Today, clinical trials are the backbone of contemporary medicine. Randomized, double-blinded, placebo-controlled clinical studies are critical for the advancement of medicine and the field of dermatology.

Overview of clinical trials

Between 2005 and 2012, the FDA approved 188 new therapies for 206 indications on the basis of the results from 448 trials (Downing et al., 2014). Clinical research has led to the development of effective and life-changing treatment for cardiovascular and autoimmune diseases, skin conditions, diabetes, cancer, and an array of diseases that affect patients worldwide.

Results from clinical trials have significantly improved the outcomes and quality of life of patients with dermatologic conditions.

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Since 2011, eight new therapies have been approved by the FDA for the treatment of patients with metastatic melanoma, including four immunotherapy agents and four targeted therapies. Since the early 2000s, targeted immunotherapy for patients with psoriasis has become a strong focus in clinical research and resulted in the development of new therapeutics on a yearly basis and half a dozen agents that are currently under development.

Skin conditions are among the most common health problems in the United States and one in three people are affected at any given time, which is more common than obesity, cancer, and hypertension (Bickers et al., 2006). Dermatologic diseases increase both direct and indirect medical costs and present a challenge to the quality of life of affected patients. In addition to the clinical presentation, skin conditions can also manifest as severe pruritus and cause impaired movement and debilitating emotional effects (Bickers et al., 2006). Psoriasis, for example, is an autoimmune skin disorder that severely impacts health-related quality of life (Rapp et al., 1999) and patients report reduced physical and mental functioning that is comparable with that of patients with cancer, arthritis, hypertension, heart disease, diabetes, and depression. Measures of treatment efficacy within clinical trials should not only focus on clinical improvement but also incorporate patients' perceptions of quality of life improvement to more holistically treat the psychosocial aspects of dermatological diseases (Charman et al., 2003).

The clinical trials unit

To maximize safety and efficacy, clinical trials are conducted in four separate phases. Phase I trials are initial tests on a small group of human subjects to determine treatment safety, dose range, and potential side effects (Collier, 2009). Phase II trials are conducted on a larger group of people to determine treatment efficacy (Sedgwick, 2014). Phase III trials involve the randomized and controlled multicenter study of even larger populations to determine and confirm the effectiveness of the treatment or drug in question (Sedgwick, 2014). Lastly, Phase IV studies typically occur after marketing of the product and assess the long-term adverse events and effects in varying populations (Collier, 2009).

Clinical trials can be conducted at academic medical centers and in private practice settings. Typically, the study sponsor is a pharmaceutical company that studies a drug, treatment, or device with the goal of marketing the product to the public. The pharmaceutical industry has financially sponsored and supported approximately two-third of all clinical trials in the United States between 2008 and 2013. This estimate is even higher for studies that were conducted in the field of dermatology (Campa et al., 2016).

Every study team includes a clinician who serves as the principal investigator (PI) who is responsible for the study conduct and oversight of the research activities. First, the PI is approached by a pharmaceutical company to determine the PI's interest in conducting the research and generate an initial contract. Next, the PI signs a confidentiality agreement to assure nondisclosure of any proprietary information that is related to the research. The sponsor of the study will then assess, through a questionnaire and communication with the PI, whether the trial can be conducted at the PI's site. The questionnaire surveys the investigator's experience, information on the site and patient population, and provides the PI with the full study protocol to determine whether the physician can feasibly conduct the study with use of the facility, available resources, and support staff. After this information is collected, sponsor representatives conduct a preliminary onsite visit to confirm that the site is adequate to support a trial, including an onsite review of space for storage of study records and study drug and the study protocol with personnel who are involved in the trial. After selection of the trial site, multiple PIs and coordinators convene during an investigators' meeting to discuss details of the protocol and exchange information about the study (Carson, 2006). It is also important for the PI to be aware of the hypothesis or question under evaluation and whether it aligns with what Bagatin and Miot (2013) refer to as the feasible, interesting, novel, ethical, and relevant (FINER) criteria.

The next critical step before initiation of the study is approval by an institutional review board (IRB). The study site must submit documents with regard to the study protocol, patient informed consent, drug and/or treatment to be studied, and other relevant details to protect the subjects who will be recruited for the study. IRB approval can present a challenge to research sites that initiate studies because it can significantly delay the start of a trial. Check et al. (2013) reviewed literature in support of a centralized IRB approval process instead of the common local IRB approval process and found that there are proponents of both procedures. Proponents of the centralized IRB review value consistency among sites and those who prefer the local review process raise concerns about the loss of quality of the review and of the emphasis on the context of the local community (Check et al., 2013).

Informed consent documents are also critical to initiate a study and provide study subjects with the information they need to make a well-informed decision about participation in the trial. Once the IRB approval process is satisfactorily completed, the PI will submit multiple regulatory documents and a clinical trial agreement to indicate the sponsor's responsibility to fund the trial. The site initiation visit is the final step before subjects can be enrolled in the study. Study representatives at the site will receive all the necessary equipment and documents from the sponsor and meet with the clinical research associate who will monitor the study throughout the course of the trial. Once a site is fully approved and initiated, enrollment of subjects can begin (Carson, 2006).

For all trials, one main concern of investigators is subject recruitment, especially at sites that do not have an adequate patient population for the study in question. Some academic centers rely on a patient registry or database to find potential study subjects (Bain, 2005) whereas others use broadcast messaging techniques, flyers, letters, phone calls, and presentations to health care providers (Aitken et al., 2008). Recruitment is crucial to the success of the study because without patients, there is no trial. If the overall target sample size is not achieved, the study can be “underpowered”, which may potentially jeopardize the validity of the results (Gardner et al., 2016).

In addition to a clinical trial site with facilities, qualified principal investigators, proper study protocols, and recruitment strategies, the last requirement is to fill the crucial role of study coordinator. Often, registered nurses are assigned this role in randomized clinical trials (Mueller, 2001). Study coordinators serve as clinical interpreters and patient advocates throughout the course of the trial (Sadler et al., 1999) and are well versed in all aspects of the study protocol, initiate the recruitment of patients, and ensure the clinical care of all subjects. They also record important data from the study subjects in case report forms, assist investigators with skin assessment records, monitor and report serious adverse events, process tissue specimens for laboratory testing, conduct the informed consent process, and schedule all patient visits that last several hours (Green, 2011). Not only do coordinators need to possess clinical skills to take care of study patients including administration of the study drug if needed but they must also have critical thinking skills to manage the complex ethical, regulatory, and scientific nature of the trial (Green, 2011; Hastings et al., 2012). Study coordinators manage all dimensions of study trials as well as focus on all aspects of patient care. As noted above, without patients, there would be no trial, and likewise, without coordinators, there would be no study patients. They are an invaluable resource to the clinical trial team.

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