

Preface

Introduction

Welcome to the arena of clinical investigation in dermatology. As a physician, you are in command of a variety of marketable tools, techniques, and skills. Whether you are in academic medicine, work in a multispecialty group, or are in a single-specialty dermatology practice, you might be interested in broadening your horizons by embarking on an adventure in clinical discovery. You may be interested in working on your own, or with others in the large and expanding opportunities in dermatology pharmaceutical and device research. This book is a comprehensive guide to taking your first steps in dermatology clinical trials.

The Benefits of Clinical Research

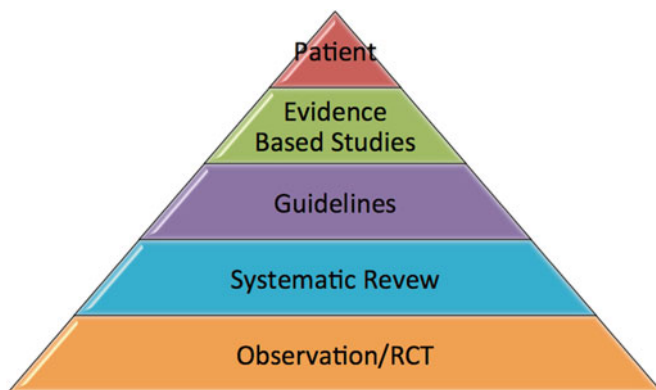
When you make the decision to conduct clinical trials, you will learn that it is something you can accomplish in a variety of ways. You may belong to a large academic medical center or university. Your department or institution may already have an affiliated investigative facility. There may be established dermatologists within the facility, or you may, as the only dermatologist, expand the scope of responsibility of the facility. You may be in solo private practice or part of a single- or multi-specialty clinical practice. Your location may not offer any clinical research at all, and you may be the first to set up and establish a niche in dermatology research among your immediate colleagues. You may be interested in a career in government, at a clinical trial unit at the National Institutes of Health. You may be interested in writing protocols and overseeing clinical research at a pharmaceutical company. Alternatively, you may be entrepreneurial and intend to set up your own company based on research you do.

Whatever route you take, and whatever the goals you wish you achieve, when you actively engage in a clinical research enterprise, you join a national and global com-

munity of driven and talented dermatologists who derive great pride, satisfaction, and intellectual stimulation from the work that they do. You will interact closely with scientists, technical experts, and a variety of staff in moving cutting-edge research forward in a standardized and safe manner. You will add to your knowledge of the basic biology of disease. You may sharpen your clinical skills by learning the latest advances and protocols. You will meet colleagues and make many friends in private practice, clinical research centers, academia, industry, finance, the media, and government. You may publish and present some of your findings and local, national, and international conferences. In addition to diversifying your revenue stream, you will diversify the treatment options you can offer patients and referring colleagues in your community. You may enjoy investigative dermatology so much that you may embrace it full time.

Bottlenecks in Drug and Device Development

Industry, the government, and your patients need you. The main reason is that development of drugs and devices is impeded by ever more and ever narrowing bottlenecks. These bottlenecks stem from competing priorities among regulators, drug and device developers, patients, the public, governments, investors, and society. Bottlenecks are costly and frustrating to developers and to patients. Patent clocks tick on every compound or device from the moment the patent is filed. The sooner a drug or device is approved, the longer a drug or device maker has patent exclusivity and the greater revenue the maker can recover to offset the costs of research and development. Tight bottlenecks mean long approval times, abbreviated patent exclusivity, and diminished revenue. Longer approval time may also give a rival a chance to create a competitive product, further eroding the value of a patented drug or device. Industry, shareholders, and impatient investors often exert pressure on business decisions and may terminate research on an otherwise promising breakthrough because of economic ramifications years down the road. Patients ultimately suffer. Benefits of new research getting from the bench to the bedside are delayed, or tabled.



Engaging in clinical research is all about the patient. Many years of effort from many quarters must converge to ultimately benefit patients. Observational studies and randomized controlled trials generate results which, in systematic reviews, lead to clinical guidelines. These are refined in key evidence based studies to become the latest standard of care.

The Investigator Shortage

Dermatology is suffering an acute shortage of clinician investigators. The timing could not be worse for industry or better for investigative dermatologists. Now that the pace breakthroughs are reaching an inflection point in a curve shooting upward, dermatologists are either not entering clinical research or not renewing their research contracts. New drugs and devices using advanced technology—including nanotechnology—are being discovered at a rapid rate and are languishing in a bottleneck between research (the preclinical research phases of drug discovery and animal studies) and development (clinical trials). The ampersand between R&D may as well be a bottleneck twisting itself into a pretzel.

Clinical trials are expensive, time-consuming, and absolutely essential to marketing approval of pharmaceuticals and devices. High quality investigators in dermatology are needed to gather the data necessary for submission to the FDA and other government bodies. Only a large cadre of capable, qualified, and enthusiastic dermatology investigators can increase the throughput of clinical trials, reduce costs, and speed the time to market breakthrough drugs and devices.

There are other reasons for drugs and devices not making it to consumers, but a principal one is investigator shortage. Training in medicine and board certification in dermatology are long, arduous processes. Debt obligations limit career choices. Additional training required for investigative dermatology may not appeal to everyone. The challenges and administrative burdens of conducting clinical trials are growing. Protocols are more complex. Regulations are more cumbersome. Some investigators only complete one trial in their lifetime, never bothering to seek additional studies. This shortage is felt so acutely in industry that at least one company (Galderma) has established an in-house investigative dermatology fellowship in order to train the next generation of clinical researchers. The National Institutes of Health has several programs to encourage young dermatologists to pursue a career in clinical research. There are several university-sponsored dermatology research training fellowships in the USA as well as online courses sponsored by academia (CITI) and the government (<http://www.fda.gov/Training/default.htm>). By becoming an investigative dermatologist, you will be a key contributor to the solution.

Tectonic Shifts in Research

There are many routes to becoming a clinician investigator. Even if you have not completed a government or industry-sponsored clinical research fellowship, or are not on faculty at a major academic medical center, you can still begin a successful career as an investigative dermatologist. In fact, for a number of reasons, there has been a shift to move clinical research out into the community. The preponderance of investigative dermatologists in the twenty-first century is now in private practice or directors of clinical research centers. This is true in the USA and globally, where more and more trials are conducted.

Good Clinical Practices

This book will go over what you need in order to establish yourself as an investigative dermatologist overseeing trials on human subjects. You will acquire the basic knowledge you need to conduct studies safely and in accordance with internationally recognized principles and practices. You will learn that clinical trials require sponsorship, whether from grants or contracts, whether from the government or industry. You will learn that sponsors will require you to have minimum qualifications as an investigator. One of the chief qualifications is a solid grasp of good clinical practices (GCP). GCP is not about taking care of dermatology patients. It's about adhering to universal practices for the protection of human subjects, for the collection of data, and for documentation of data in a format acceptable to government regulatory agencies for approval.

Regulatory Bodies

You will learn about the key players in regulation. The Food and Drug Administration (FDA) has three major sections which regulate innovations in dermatology. The Center for Drug Evaluation and Research (CDER) oversees drug developments. The Center for Biologic Evaluation and Research (CBER) oversees vaccines, therapeutic sera, toxins, antitoxins, blood and blood products, allergens, immunoglobulins, cytokines, and biotechnology-derived products such as cell-derived products or recombinant DNA-derived products. The Center for Devices and Radiological Health (CDRH) is responsible for ensuring the safety and effectiveness of medical devices and minimizing unnecessary exposure to radiation-emitting products. You will learn how these agencies oversee research and protect the public.

Practical Tips

You will learn about the history of clinical investigation. You will understand the regulations governing clinical research in that historical context. You will learn about the drug and device discovery process from initial idea to final approved product. You will learn about post-marketing surveillance to detect and measure unforeseen benefits and risks of approved products. You will also learn the nuts and bolts of running investigative sites. You will learn how to solicit sponsorship for ongoing or new trials. You will learn what qualities sponsors and granting agencies look for in order to consider you a potential investigator. You will learn what to look for when considering a potential sponsor or research project.

Contracts and Budgets

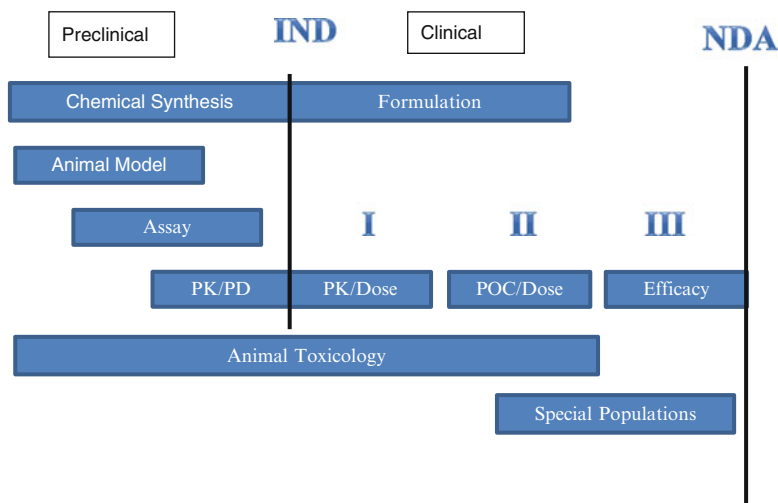
You will learn how to negotiate contracts and budgets. You will learn how to do a study feasibility analysis. You will learn how to spot studies that are right for you and how to say no to the ones that are not. You will learn about contract pitfalls such as publication embargoes and intellectual property. You will learn the practical details of implementing a study from standard operating procedures, managing study materials and documentation, recruiting and retaining volunteers, dealing with adverse events. You will be informed on regulations governing research that you do and the training requirements for you and your staff. You will learn about the hazards of Anti Kickback Statutes, Stark Laws, and privacy laws such as HIPAA. You will learn how to work with contract research organizations and site management organizations.

Perspective

You will learn about important ethical issues for you and various players in your research team. You will learn about vulnerable populations in clinical dermatology. You will gain an industry perspective on investigative dermatology. Finally, you will learn about opportunities for conducting clinical research in dermatology.

Welcome

If you are already part of an established research enterprise, once you have completed your training and certification, you will be ready to solicit or participate in trials. If you are setting up a new site, you will need to make your entity legal and compliant with regulations, assemble your team, and outfit your facility. Using the resources described in this book, you will be able to develop your network to become a sought-after investigator in dermatology clinical trials. You will be the first to glimpse treatments at the limits of science. Welcome to dermatology beyond the horizon.



From bench to bedside, drug and device development can take 10–15 years. The preclinical phase includes characterization of compounds and entities, the development of animal models and assays, animal toxicology studies, pharmacodynamics, and pharmacokinetic studies. Clinical trials in human subjects are the linchpin of the whole process.

Early Development: This is the preclinical in vitro, in vivo, or in silico phase. Once these studies are done, permission to test in humans is given by the FDA via the IND (Investigational New Drug) application. This application has an outline for the proposed studies. Once the application is filed, the clock starts ticking, as the patent is good for 20 years.

Phase I: 20–100 healthy volunteers are given increasing doses to test safety, tolerability, PK, and PD. The dose is 1/10th of the human equivalent dose where NOAEL (no adverse effect level) is seen in the most sensitive species in two different animal studies. During this phase, factors which affect absorption, metabolism, and excretion of the drug are evaluated. Microdosing or phase 0 trials can be substituted for this phase.

Phase II: In Phase II trials, the test agent is given to larger groups of people (200–300) to see if it is safe. This may also be the dose-finding phase. In Phase II trials, because there are larger groups of subjects, they may have varying degrees of illness and the variety of responses as well as a variety of toxicities can be observed in this phase. Sometimes comparison drugs or placebos are tested in this phase.

Phase III: Broadens the population receiving the drug, including more real-world subjects with other underlying illnesses. Sometimes the drug is tested against placebo. It is unethical and illegal to give a placebo to seriously ill patients if alternative therapies are available. Hence, these studies have comparator drugs. This phase,

which gathers more safety and dosing evidence, is required before submitting a New Drug Application (NDA). These trials often involve thousands of patients and are multicentered. At least two successful Phase III trials are required before FDA approval. This is less stringent for oncology, where one trial is required. Because this phase is so important to a medication's success, an independent DSMB (Data Safety Monitoring Board) is enlisted, especially if the study team's members are blinded, to alter the trial, or halt a trial because of safety concerns or because one group is doing substantially better than another.

Phase IV: Typically done for marketing purposes rather than intellectual curiosity. These trials compare an approved drug with a major competitor. This phase can also change a medication's status from prescription to OTC. It can also target genders, ages (pediatric population), and ethnicities.

Post-marketing surveillance can pick up unexpected serious side effects (thalidomide, Ketek), which can lead to withdrawal or additional warning labels. Some of these side effects and toxicities may go undetected because of small numbers (ICH requires approximately 1,500 subjects; most adverse events occur in the first 6 months, so you need 300–600 patients for that time to detect events at a frequency of 0.5–5 %; to detect AEs of 1 %, you need more than 100 patients for more than a year).

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