

Chapter 2

General Clinical Trials

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2.1 Design of Trials

There are different types of clinical studies (Fig. 2.1). They can be divided into observational and clinical trials (interventional). Observational studies include cohort studies, in which a group of subjects are followed to analyze potential risk factors for developing a disease; case control studies, in which one group of people who have the disease of interest and another group who do not have the disease are compared to identify potential risk factors; and cross-sectional studies, in which an entire population is observed at one point in time to determine data such as disease prevalence or risks [1]. Observational studies offer helpful information regarding associations that may exist between certain exposures and outcomes. This information would be useful if a researcher is trying to determine if a group of people with a common exposure have a change in the risk of developing a certain disease [2]. For example, a case–control retrospective study by Robinson et al. sought to investigate whether the use of photosensitizing medications increased the likelihood of developing non-melanoma skin cancer. This observational study examined people who had a form of non-melanoma skin cancer (case) as well as those who did not (control), and determined how many from each group had been exposed to photosensitizing medications. The data showed that the use of photosensitizing medications may increase the risk of developing a form of non-melanoma skin cancer [3]. Because this study examined exposures from the past, it is considered a retrospective study. Studies that examine a present exposure and measure future outcomes are called prospective studies and they, too, offer useful information regarding links between exposures and outcomes [2]. Chen et al. conducted a prospective cohort observational study by identifying patients who had a

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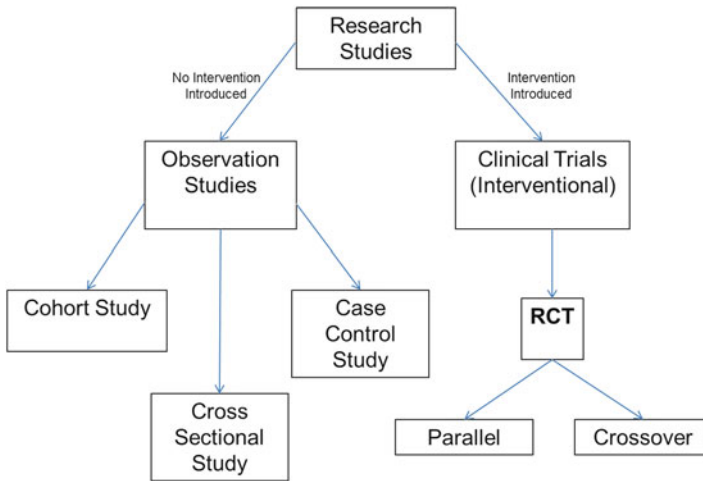


Fig. 2.1 A simplified overview of research study designs. Observational studies, where no intervention is introduced, include cohort, cross-sectional, and case control studies. In contrast, interventional trials include an intervention of interest and are most commonly designed as randomized control trials (RCTs) which can utilize parallel or crossover treatment and placebo groups

non-melanoma skin cancer that was treated either by electrodesiccation/curettage, general excision, or Mohs excision. These patients were followed to identify any recurrences of their skin cancer in an effort to determine if any of the treatment methods was superior in terms of reduced recurrence rates. The data collected showed that the difference in recurrence rates among the treatment methods was not statistically significant, which demonstrates that observational studies can help answer relevant research hypotheses [4]. However, while observational studies yield useful data, they utilize natural conditions and are not designed for clinical trials where medical treatment is introduced. Naturally, experiments are used to design clinical trials in which some form of intervention is studied [2]. The gold standard of an interventional clinical trial is the randomized controlled trial (RCT) [5]. RCTs are often considered the “gold standard” because it is the only proven method that can reduce bias by ensuring that those receiving the study treatment and those receiving placebo are as equal as possible in regard to known and unknown variables [6]. To bolster this claim, Schulz et al. credit randomization, avoidance of exclusions after entering the trial, and blinding as the keys to the RCTs superiority. They go on to state that studies that do not include these three criteria tend to generate questionable data [7]. Sackett et al. further support the idea that RCTs are the gold standard of clinical trials because they frequently provide useful outcomes and are so rarely misleading [8]. However, certain biases have recently questioned the validity of RCTs. As an example, a study of five empirical methodological studies has shown that RCTs that produce positive results, meaning that the item or drug under study in the RCT did produce a statistically significant result, are more likely to be published and published quickly than RCTs that create negative results, meaning the item or drug under study did not produce a statistically significant result. This effect is known as publication bias, and it argues that

because RCTs that produce positive results are more likely to be published, the RCT is itself a biased method of reporting data [9, 10]. Regardless of these arguments, however, RCTs are still widely used for designing clinical trials.

Inset 2.1

Example of a randomized trial:

Clobetasol propionate, 0.05 %, vs hydrocortisone, 1 %, for alopecia areata in children: a randomized clinical trial. Lenane P, Macarthur C, Parkin PC, Krafchik B, DeGroot J, Khambalia A, Pope E. JAMA Dermatol. 2014 Jan;150(1):47–50.

In this single-center trial, a low- and high-dose topical steroid were compared over a 24-week period on children ages 2–6 with alopecia areata of the scalp. The trial was blinded in a 2-arm parallel group. Topical steroids were applied for 6 weeks on and 6 weeks off for two cycles during the 24-week study period. The primary endpoint assessed was hair loss at the end of the study. Investigators noted a greater decrease in hair loss in the high potency group compared to the cortisone group. One subject in the high potency group had atrophy which resolved in 6 weeks. No systemic cortisol disturbances were observed.

In RCTs, two groups of patients are established: those receiving the treatment being studied, and those who do not receive the study treatment, but rather a placebo (or a previously established treatment) [2]. The advantages of this design allow for bias reduction through randomization [5]. Bias occurs when different variables such as age or gender are not balanced between patient groups and therefore sway trial results. Randomization refers to a patient being randomly assigned to either the treatment group or placebo (control) group once they have been screened and identified as being eligible for study participation [11]. Randomization reduces bias by randomly distributing these variables, ideally equally, between the groups [6].

Inset 2.2

Blinding or Masking

In a study of hypnotism, or mesmerism, Benjamin Franklin, and Antoine Lavoisier blindfolded (or masked) subjects to prevent them from seeing treatments before evaluating the claimed results. Though used interchangeably with blinding, masking implies eye openings and the ability to see what is going on. Because of potential confusion, blinding has become the standard term in the international clinical research lexicon.

Franklin B, Bailly JS, Lavoisier A. Rapport des commissaires chargés par le roi, de l'examen du magnetisme animal. Chez Gabriel Floteron: A Nice; 1785.

RCTs can be further modified by their design and degree of blinding. RCTs typically utilize a parallel-group design in which the two groups remain separate in their treatment setup, but everyone within each group is treated identically. Crossover studies are studies in which each patient receives both the study intervention and the control for equal but separate time periods. These also offer the benefit of further bias reduction since each patient serves as his own control [12]. Also critical to the design of a RCT is the blinding status. In a single blind RCT, the investigator is aware of a patient's treatment status, but the patient is not [11]. This design leaves the data vulnerable to experimenter's bias in which the investigator's knowledge of treatment status could influence his evaluation [13]. Double-blind studies eliminate this bias, as well as the placebo effect, because neither the investigator nor the patient is aware of treatment status [11]. An outside participant, typically an unblinded pharmacist, is the one who is aware of the patient's treatment status. An understanding of how RCT design and blinding allows investigators to develop the RCT that will investigate their hypothesis while limiting the degree of bias involved.

Inset 2.3

Example of a multicenter DBPCR randomized.

Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria.

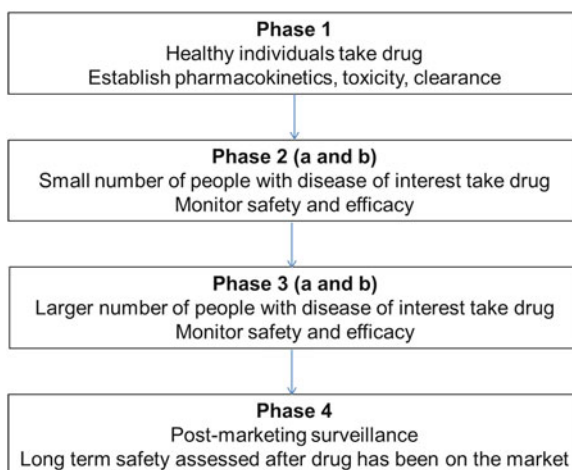
Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Giménez-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. *N Engl J Med*. 2013 Mar 7;368(10):924–35.

This was a phase-three trial to evaluate the safety and efficacy of omalizumab in anti-histamine refractory chronic idiopathic urticaria. Volunteers were randomly assigned to receive drug at three different doses, or placebo, followed by a 4-month observation period. They were asked to score their itching. The baseline itching score was 14 in all four groups. It dropped to 9 in the placebo group, 8, 6, and 4 in the 75 mg, 150 mg, and 300 mg groups, respectively.

2.2 Phases of Drug Development

For a new drug to be approved by the FDA for commercial use, it must undergo a series of trials (Fig. 2.2). The process begins when a new drug is developed in a laboratory setting. Laboratory testing usually begins with cell studies, and ultimately graduates to live animal studies to determine *pharmacokinetics* and *toxicity* [14]. For this preclinical testing data to be considered acceptable to the FDA, it must comply with good laboratory practices (GLP). Adhering to GLP ensures that the data produced in the laboratory studies meet the minimum environment, personnel, and technique standards necessary to ensure reliable data. The specific goals that contribute to a successful preclinical trial include understanding basic

Fig. 2.2 A diagram of study progression. All investigational drugs or products that pass preclinical testing and are reviewed by the FDA are first tested in a phase 1 clinical trial and then progress to phase 2 and 3 trials. Once approved by the FDA, phase 4 studies continue to monitor the product for long-term safety purposes



pharmacokinetics of the drug, identifying drug toxicity levels in two different species of animals, and performing short-term toxicity studies that are approximately equal in time length to the actual drug treatment time [15].

Once acceptable standards are met in animal models, the drug is then studied in humans. This begins with a *Phase 1* trial in which a small number of healthy individuals take the drug. These participants are then studied to further establish pharmacokinetics and toxicity as well as drug clearance in humans. Again, once an acceptable standard is met, the drug passes to a *Phase 2* trial where its **safety** and **efficacy** are measured in a small number of patients who have the disease the drug intends to treat [14]. Of note, Phase 2 trials can be split into Phase 2a and Phase 2b trials. Phase 2a trials focus on proving the suspected mechanism of action of the drug and typically involve fewer patients than Phase 2b trials. Phase 2b trials strive to identify the ideal dosage of the study drug that allows for the desired efficacy while minimizing side effects [16]. If the drug is shown to be effective for the disease of interest, it is then tested in a *Phase 3* trial. Phase 3 trials continue to demonstrate efficacy and safety in patients who suffer from the disease of interest, but involve a much larger patient population and test the drug at different concentrations as well as in combination with other medications [14]. Similarly to Phase 2 trials, Phase 3 trials can be split into Phase 3a trials where the main goal is to generate sufficient data to demonstrate safety and efficacy, and Phase 3b trials which seek to support future publications [16]. Finally, when sufficient data has been collected, the sponsor of the drug submits a new drug application (NDA) to the FDA for final approval. *Phase 4* trials, or *post-marketing surveillance*, are conducted after an approved medication is on the market in order to test long-term safety of the medication [14].

Under the FDA Amendments Act (FDAAA) of 2007, pharmaceutical companies are tasked with maintaining standards of transparency regarding their study data. The main goal of the FDAAA was to ensure that the FDA received the necessary resources to review new trials; however, the act also impacted the degree of transparency of sponsor-initiated clinical trial data. The FDAAA requires “disclosure of any restrictions on public presentation or publication of results of studies funded by industry”

[17]. Now drug companies are required to make available to the public, information and results regarding their clinical studies, regardless of the stage of drug development. Most industries list their studies and relevant information regarding the studies and medications on their website so that the public can learn more about the methods, goals, and safety of current research. The public can also learn more about the multitude of clinical studies being performed by visiting www.clinicaltrials.gov.

2.3 Evolution of US Drug Law

Essential to the development of clinical trials are the drug laws that have established an acceptable degree of safety and efficacy for newly manufactured drugs. The first form of organized US drug law was developed in 1820 with the establishment of the US Pharmacopeia (USP), the first official list of standard drugs used in the United States [18]. Over time, the laws have evolved to keep up with advancement in science and engineering (Table 2.1). However, their goals remain the same—to ensure the efficacy of new investigational products as well as the safety of the patients who contribute to their development. Certainly their influence on clinical trials warrants a brief discussion of the history of their evolution and impact.

Before the direction and organization offered by drug laws existed, drug manufacturers didn’t follow a standard protocol; this led to inconsistencies in drug development and sanitation. The consequences of these practices came to national attention in 1901. At that time, scientists were developing diphtheria vaccines by injecting *Corynebacterium diphtheriae* into horses and collecting their antibody-rich serum. However, due to a lack of sanitary protocol, thirteen children were killed after they were accidentally exposed to tetanus toxins incurred from this practice [19]. The tragedy led Congress to establish the Biologics Control Act, which was tasked with overseeing the safety and purity of vaccines. Five years later, the Biologics Control Act was molded into the Pure Food and Drugs Act of 1906 by then-president Theodore Roosevelt with the goal of blocking foreign trade of “mislabeled food and drug products” and prosecuting those who were found guilty of these practices [20].

1820	US Pharmacopeia established
1902	Biologics Control Act
1906	Pure Food and Drugs Act
1911	US vs. Johnson
1912	Sherley Amendment
1927	Bureau of Chemistry Splits
1930	Regulatory Branch of Bureau of Chemistry is renamed FDA
1962	Kefauver-Harris Drug Amendments Act
1983	Orphan Drug Act
1998	Pediatric Rule
2003	Pediatric Research Equity Act

Table 2.1 Brief timeline of US Drug Law Evolution

The law also required that each drug should have a label of active ingredients and should maintain a minimum drug purity level set by the US Pharmacopeia [21].

Whereas early US drug laws focused on purity and safety in manufacturing of drugs, more recent drug laws have focused on the importance of data from clinical trials in establishing the potential for adverse events and drug safety. In 1962, a new drug, thalidomide, gained popularity in Europe for its use as a sedative as well as an off-label use as a cure for morning sickness during pregnancy. However, doctors soon discovered that thalidomide was responsible for thousands of infants being born with phocomelia, or dysmorphic limbs [22]. Fortunately, the Food and Drug Administration (FDA) had not given approval for this drug due to FDA inspector Frances Kelsey's demand for data from clinical trials and for more convincing evidence that the drug did not cross the placenta [23]. The disastrous outcomes from this ordeal led to the development of the Kefauver-Harris Drug Amendments Act of 1962 which increased monitoring of drug approval processes as well as required clinical trial data demonstrating the safety and efficacy of new drugs before drugs could be approved.

After drug laws addressed the need for legitimate data from clinical trials for drug development, they shifted to focus on the different needs of specific patient populations. For example, in 1983, the Orphan Drug Act was passed which allowed the FDA to promote research for drug development for particularly rare diseases since they would otherwise not receive much attention [20]. Since this act passed, orphan drugs have continued to receive increased attention. As an example, the National Institutes of Health (NIH) has created the Therapeutics for Rare and Neglected Diseases (TRND) program that offers incentives for collaborators, including academic scientists, non-profit organizations, and pharmaceutical companies, to apply to work with NIH research teams to promote research efforts for new orphan drugs. The overall goal of these collaborations is to expedite the time necessary for a new drug discovery to progress through preclinical testing so that it may be a suitable project for pharmaceutical companies interested in developing the necessary clinical trials [24, 25]. In 1998, the FDA promoted the Pediatric Rule which extended the mandates of the Kefauver-Harris Drug Amendments Act to drugs that would be applicable to pediatric patients. This, in combination with the Pediatric Research Equity Act of 2003, which grants the FDA authority to mandate that sponsors conduct research for pediatric applications of investigational drugs, ensured that research for new drugs adequately addressed the needs of pediatric patients [20]. Obviously, medical knowledge continues to expand and offer new therapies to different patient populations. Just as important, however, is the fact that drug laws continue to evolve and direct drug development to protect the patients who need them.

2.4 How to Initiate Clinical Trials or Start a Clinical Research Site

There are three main characteristics that Sponsors and contract research organization (CRO's) look for in a site that is interested in doing clinical trials: the principal investigator (PI) qualifications, site adequacy, and patient population.

2.4.1 *PI Qualifications*

You don't have to be in an academic institution to become a PI. In fact, by 2005, 70 % of all the clinical trials in the United States were done in a private practice setting [26]. Several reasons for this shift are: the lower cost and administrative burdens in private practice settings and the gag clause (that prevent investigators from utilizing, analyzing, or publishing data from the trial without consent of the Sponsor) [26, 27]. Regardless, you should be able to prove that you are a good candidate. What steps should you follow?

- (a) *Gather information and learn the basics of clinical research trials*: Read books (reading this book is a good start); utilize online resources; understand good clinical practices (GCP) and get formal training if needed. There are a wide range of training opportunities available from conference sessions to fellowship programs and even new master's degree programs in clinical research targeting MDs (see "Useful Links" in References section).
- (b) *Do some networking*: Talk to the medical representatives about your interest in clinical trials; they will be able to direct you to the proper persons in their companies. Stop by the pharmaceutical booths in your medical organization meetings and meet the medical liaison team. Register online for the different Sponsors' investigator databases. Join or attend a clinical research organization such as the ACRP (Association of Clinical Research Professionals), SOCRA (Society of Clinical Research Associates) or the MAGI's (Model Agreements & Guidelines International) Clinical Research Conference.
- (c) *Show your experience/expertise*: Your curriculum vitae (CV) or resume should reflect your experience as a clinical investigator. Start as a sub-investigator with a mentor. If you don't have any experience, do you have a particular area of expertise? Do you have publications that support your experience in that particular field?

2.4.2 *Site Adequacy*

You should have dedicated clinical trials space for equipment and supplies and sufficient staff qualified to perform the different tasks required by the study protocol.

- (a) *Facility*: You need to show the Sponsor or CRO that your facility is suited to conduct a clinical trial. This includes enough space to conduct the visits and ensure the privacy of the subjects. Specific requirements are listed on Table 2.2. If you don't have laboratory facilities you may be able to use a nearby laboratory to draw blood and process samples. It is important to have a multidisciplinary network in case the protocol calls for specific assessments such as X-rays, ophthalmologic evaluation, etc.
- (b) *Staff*: The success of a clinical site depends on having an engaged, enthusiastic, interested PI and a knowledgeable, experienced study coordinator. The PI should have committed time for research including (but not limited to) perform-

Table 2.2 Site requirement

(a) Adequate files, cabinets, storage space
(b) Refrigerator for storage of the investigational product
(c) Thermometer to monitor refrigerator temperature
(d) –20° freezer to store blood samples
(e) Access to dry ice
(f) Computer with internet
(g) Copier and fax machine

Inset 2.4

The Sponsor Team

- *Clinical Research Associate (CRA):* The CRA is also called the monitor. Budget time to meet with the monitor and try to make a good impression. A typical trait for a monitor to have is compulsive attention to detail. The frequency and intensity of monitor visits vary with the experience of the investigative site, the complexity of the trial, and the dictates of the protocol. The monitor makes sure that your site is conducting a study according to the protocol, that your data are accurate, complete, contemporaneous, legible, attributable, original, and enduring. The monitor makes sure any deviations from the protocol are adequately explained. The monitor ensures that adverse events are promptly and correctly addressed. The monitor takes your questions and concerns back to the sponsor for feedback. Your monitor is a dedicated, knowledgeable professional, who may have even been a CRC once. Be very courteous, respectful, and attentive to your monitor’s needs. A good relationship with your monitor will make your study go very smoothly. Your monitor may also be in the loop for a variety of studies, and will likely recommend you and your site if you perform well. Pay close attention to any concerns your monitor has. These should be addressed promptly, courteously, and professionally. Your monitor knows the protocol, and has been to a number of sites to see how the protocol is executed. Any lapses or concerns your monitor observes including out-of-date training certificates or unsigned documents or disorganized documents should be taken seriously. By doing so, not only will you improve the quality and timeliness of your work, you will avoid trouble in case of an audit. You will also save money, and make your monitor and sponsor happy. Visits can last from 4 h to several days. Disorganization costs money. Monitor visits to disorganized sites take longer, and often require revisits to ensure accuracy of data. This means more travel costs and more time costs for the sponsor. Your CRA may also be monitoring several sites (typically 5–10). If your site is not organized, you will be costing the monitor time away from family and from other sites.
- *Medical Research Associate (MRA):* The MRA an in-house CRA at the sponsor’s facility. The MRA may oversee CRAs and studies and monitor

subject safety, and make sure that all procedures are conducted in accordance with the protocol. The MRA may have been a CRA in the past and may be tapped to cover for your CRA if he or she is on leave or vacation or transitioning to another study. Give the same courteous treatment to your MRA that you do to your CRA.

- *Sponsor*: This is the overall developer of the drug or device. The sponsor oversees the development of a device from its initial chemical identification all the way through manufacturing, testing, approval, marketing, and post-marketing phases. The sponsor finances all aspects of a study from designing the trial, to providing materials, collecting data, monitoring trial, auditing all procedures and data to support the application to the FDA. Sponsors also keep investigators informed about the drug, including new safety information.
- *Medical monitor*: a physician at the facility who is on call for questions about the protocol or safety issues.

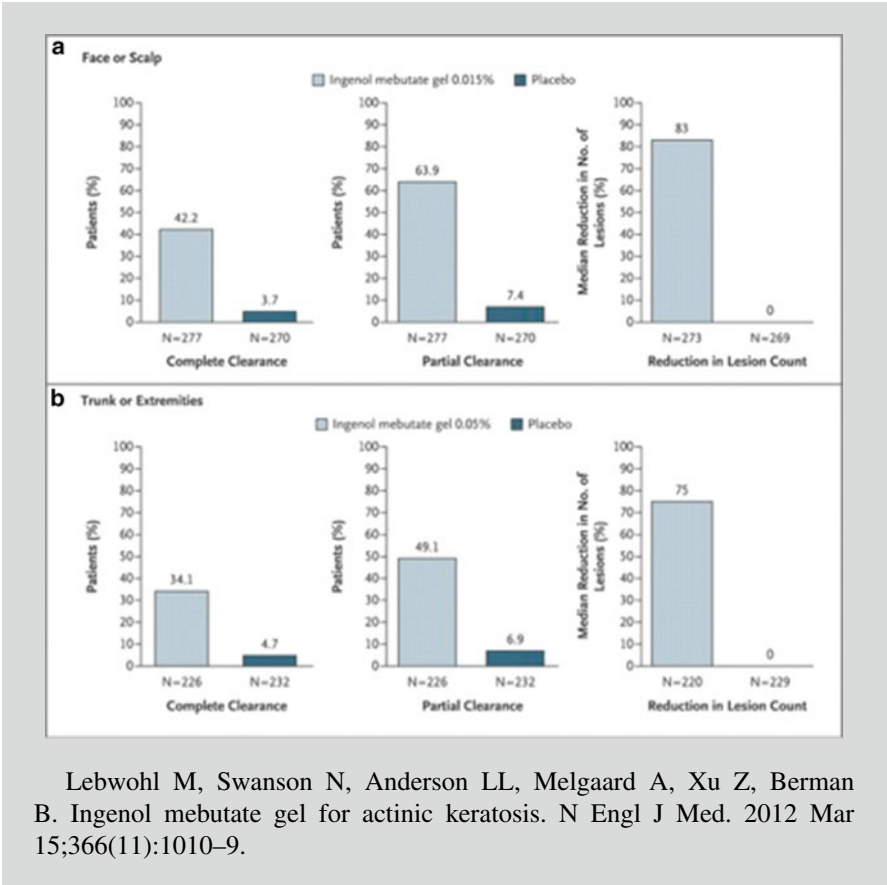
ing assessments during study visits, making time to meet with the monitors, travelling to investigator's meetings, reviewing safety lab results, and reviewing amendments to the protocol. The site should have adequate dedicated personnel to perform the protocol activities and respond to queries and requests by the Sponsors or CROs. If your study coordinator does not have experience, you could pay for them to receive formal training or certification.

- (c) *Patient population*: Sites must have the adequate study population for the particular study. Sponsors are looking for sites that can recruit and enroll subjects fast. Their goal is to do the trial in a timely manner and at the same time have high quality data and minimal queries. You should be able to answer these questions: Do you have a database of your subjects for the particular disease being studied? What is your recruitment plan? How fast can you screen and enroll the subjects?

Inset 2.5

Large multicenter trials are often complex and involve several sites. They can be expensive to conduct. They are often more time consuming for investigators because there are more documents, and adverse events to review. The trial below has pooled data from a number of sites and has a detailed Supplementary Appendix to satisfy reproducibility requirements.

Four large multicenter randomized double-blinded studies examined the response to placebo or ingenol mebutate gel. The number of actinic keratosis on either the face and scalp or trunk and extremities were assessed during the study. Data were pooled from similar skin sites and compared.



2.5 Factors Influencing Site Selection

Even if you have the qualifications, adequate facilities, staff and patient population, you may not be selected for a particular trial (Table 2.3). Sponsors and CROs are keeping metrics on every site they work with and they try to minimize unknowns when possible. Sponsors prefer to work with sites they have worked with in the past who have a proven track record. Starting clinical trials at a new site takes patience, a good work ethic, and the ability to determine if a given protocol is worthwhile.

Table 2.3 Factors influencing site selection

(a) Lack of experience of PI
(b) Time constraints
(c) Cost of running the trial
(d) Legal liability
(e) Conflicts of interest with industry
(f) Cost-effectiveness (academic sites usually cost more than private sites)
(g) Enrollment below expectations
(h) Diversity and complexity of regulations
(i) Competing studies at the site
(j) Slow IRB committee approval
(k) Lack of experience/training of site personnel
(l) Lack of specialized equipment for the specific trial

2.6 Evaluating the Feasibility of a Protocol

The site start-up process involves not only a significant amount of administrative documentation but also a critical evaluation of whether the site has the ability to perform the study as outlined in the protocol, also known as a feasibility assessment. Sites are usually contacted by a representative of the sponsor or CRO and asked to fill out a feasibility questionnaire. The questionnaire may show up in an email as an attachment or as a link to an online questionnaire that should be completed as soon as possible. The responses are used to determine if a site meets the basic requirements of the clinical trial protocol. This may involve providing basic information about PI interest in the protocol, site staff, clinical research experience, available equipment, and several questions about the patient population at that site.

2.6.1 Patient Population

It will be expected that sites provide number percentages of a given subset of patients to estimate the likelihood that a given site will be able to enroll subjects that meet the inclusion and exclusion criteria. If at all possible these numbers should be based on an analysis of the patient database as opposed to guessing. The answers provided on the questionnaire will determine if the sponsor selects a given site to move forward in the site selection process. Be mindful that the HIPAA privacy rule applies to researchers who work for a covered entity (e.g. a hospital) and therefore it is important to understand how personal health information (PHI) can be used prior to a subjects’ signing of an authorization to use PHI [28]. This rule affects institutional sites more frequently than community sites, however, protection of patient privacy is important for every site and processes should be established and documented.

2.6.2 *Site Selection*

The site selection process usually involves a site qualification visit to allow a sponsor representative or designee, a clinical research associate (CRA), time to meet with key site personnel, review the inclusion and exclusion criteria of the study, evaluate equipment, and tour the site facilities and drug storage areas. These visits not only allow the sponsor to verify the information provided in the questionnaire, but also allow the principal investigator (PI) to determine if they are truly interested in the protocol and have the staff and resources needed to be successful. The PI will likely be notified via email if their site has been selected and then be provided with a site start-up packet. The start-up packet should include the final protocol, investigators brochure, a draft budget, draft contract, all the required regulatory documents, and instructions for how the sponsor wants you to fill out and return them. Please reference Fig. 2.3 for an average timeline of the start-up process.

Inset 2.6

- **Contract Research Organization (CRO):** As the term implies, this is a groupe hired or contracted out by the Sponsor to administer the trial. Clinical trials are often the most expensive part of investigational research. To successfully usher an investigational product from the clinical phase to the marketing phase can require hundreds of research sites, thousands of study volunteers, and millions or billions of dollars. To save money, and to have a relatively fixed handle on the cost of each phase of a trial, a sponsor may hire a CRO or Academic Clinical Trials Unit (ACTU) to administer a study. A CRO may also have a niche, such as dermatology (e.g., DermTech), and provide resources and expertise to a smaller pharmaceutical company that may not have the staff to dedicate to trial administration. Working with a CRO can provide you with access to a study and help you build your portfolio of clinical research. The drawback to working with a CRO is that administrative fees taken by a CRO amount to a “tax” on your revenue.
- **Site Management Organization (SMO):** An SMO is essentially a CRO, but one that is affiliated with a site, such as a hospital or academic institution. If you are in private practice and work with an SMO, you have to make sure your contract has legal protections for you regarding intellectual property, Anti Kickback Statutes, and Stark Laws. Site management organization, manages a number of sites in its network. SMOs are also proliferating internationally, where costs are less, but where oversight is also more difficult.



Fig. 2.3 Timeline of study initiation for academic centers that may be utilizing local Institutional Review Boards (IRB). Note, the time course listed is a rough estimate. Actual times may vary depending on institution and whether or not a local or central IRB is used

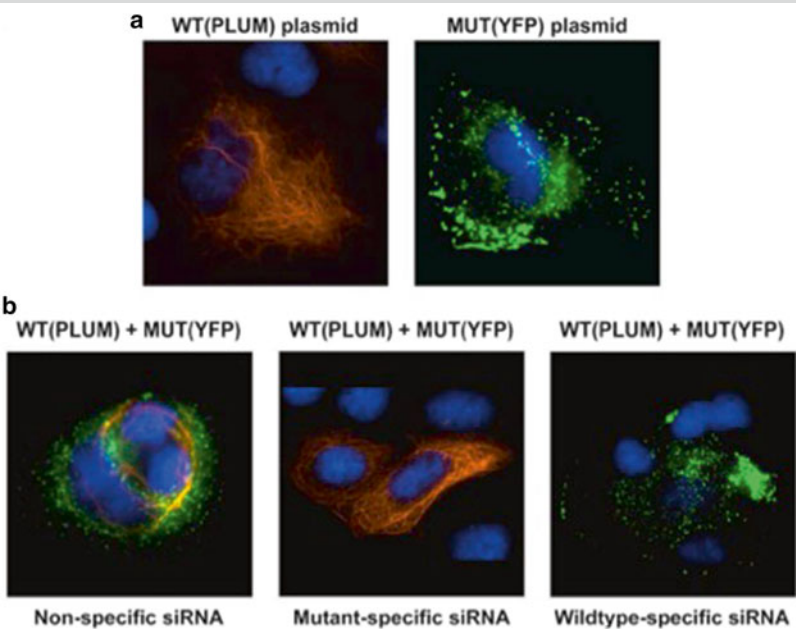
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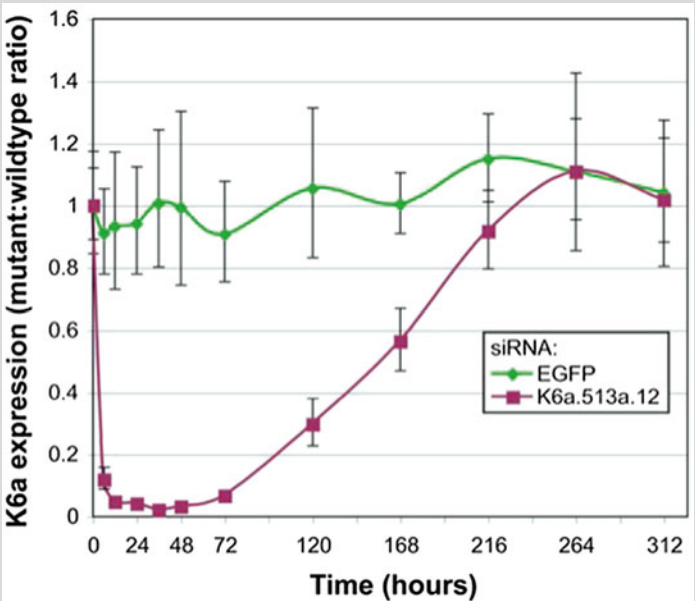
A listing of clinical trials can be found at the following web site: www.clinicaltrials.gov. An example of a pilot study on a rare genodermatosis using siRNA is a study of TD101:<http://www.clinicaltrials.gov/show/NCT00716014>.

This is a first in humans Phase I dose-escalation trial of an interfering RNA in a dominant negative genodermatosis.

Sancy A Leachman, Robyn P Hickerson, Mary E Schwartz, Emily E Bullough, Stephen L Hutcherson, Kenneth M Boucher, C David Hansen, Mark J Eliason, G Susan Srivatsa, Douglas J Kornbrust, Frances JD Smith, WH Irwin McLean, Leonard M Milstone, Roger L Kaspar. First-in-human Mutation-targeted siRNA Phase Ib Trial of an Inherited Skin Disorder. *Mol Ther.* 2010 February; 18(2): 442–446.

In vitro studies show dominant interference of keratin filament function.

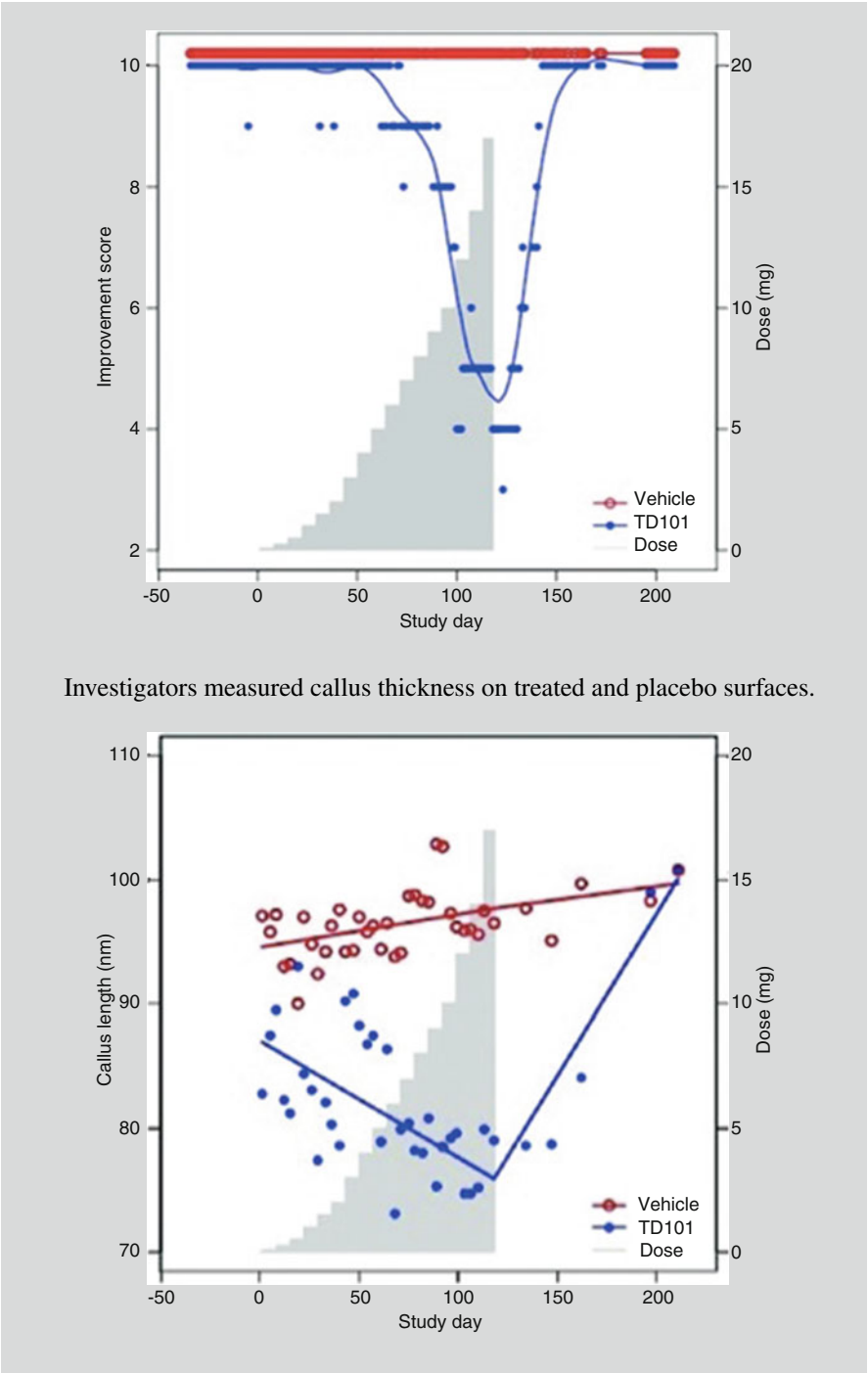




Dose of administered siRNA injected into subject lesions was escalated over 119 days, to a maximal concentration of 8.5 mg/mL and a total dose of 17 mg.

Week	Dose no.	Days	Volume (ml)	Concentration of TD101 (mg/ml)	Total dose TD101 (mg)
1	1-2	1-7	0.1	1.0	0.10
2	3-4	8-14	0.25	1.0	0.25
3	5-6	15-21	0.50	1.0	0.50
4	7-8	22-28	1.0	1.0	1.0
5	9-10	29-35	1.5	1.0	1.5
6	11-12	36-42	2.0	1.0	2.0
7	13-14	43-49	2.0	1.5	3.0
8	15-16	50-56	2.0	2.0	4.0
9	17-18	57-63	2.0	2.5	5.0
10	19-20	64-70	2.0	3.0	6.0
11	21-22	71-77	2.0	3.5	7.0
12	23-24	78-84	2.0	4.0	8.0
13	25-26	85-91	2.0	4.5	9.0
14	27-28	92-98	2.0	5.0	10.0
15	29-30	99-105	2.0	6.0	12.0
16	31-32	106-112	2.0	7.0	14.0
17	33	113-119	2.0	8.5	17.0

The patient assessed improvement of plantar skin thickness on the vehicle side and treated side.



Investigators measured callus thickness on treated and placebo surfaces.



2.6.3 Site Equipment

For Industry-sponsored studies, the sponsor generally provides for protocol-specific equipment, including for lab collection, photography, incubators (to use for quantiferon gold testing), and even electrocardiogram machines. This is not always the case, however, and so purchasing a good high megapixel camera or even a microscope for KOH testing may be in order.

Any clinic or facility where lab testing is done, even if it is only a urine pregnancy test, is considered to be a laboratory under CLIA. A CLIA certificate of waiver must be obtained in order to perform any of the CLIA waived tests. More information about how this can be accomplished and which analytes are considered CLIA waived can be found on the CMS web page [29, 30].

2.6.4 Regulatory

The regulatory documents will include at a minimum the federal form 1572 and financial disclosure forms [31, 32]. These documents are the same across all studies and constitute an agreement between the Principal Investigator and the FDA that they understand the responsibilities of conducting a clinical trial and that they have disclosed any conflicts of interest (e.g. financial stakes). Sponsors will also collect signed and dated CVs and medical licenses for the Principal Investigator and all Sub-Investigators listed on the 1572. The instructions should tell you which forms require you to send off the original signed documents after making a copy for your files.

2.6.5 Institutional Review Board Submissions

Every site must get approval from an Institutional Review Board (IRB) or Ethics Committee (EC) before they can begin research at their site. Most institutional sites (University or Hospital affiliated) will require submission to a local IRB (specific to their institution) as opposed to a central IRB which is contracted by the Sponsor to review the study for approval for all other sites not affiliated with a local IRB. The sponsor/CRO will provide the documents required to complete a local IRB submission (i.e. draft informed consent documents, recruitment materials, patient diaries and questionnaires, or patient reported outcomes). For institutional sites with a local IRB, it is important to familiarize yourself with institutional policies and procedures as these may require multiple additional submissions for review (e.g. legal department or pharmacy services). A central IRB will require each site to register by completing an application or registration form (mostly an online process). The information required can include specific information about

the site, PI, and practices to ensure subject safety. The Central IRB submission process is simple and expedient for the site as the sponsor has already submitted the majority of the study documents on their behalf. Even the informed consent document is standardized across all the central IRB sites with the exception of the PI and site contact information.

The primary purpose of the IRB is to ensure the safety and welfare of the research subjects. In conjunction with the IRB application, either the sites or the sponsor will be required to submit any and all materials presented to potential research subjects and given to subjects during the study. Most importantly, the IRB will review the informed consent forms and ensure that the language is appropriate and can be understood by the target audience.

All research personnel should have appropriate ethics training and more sponsors are requiring that all personnel have ICH GCP training that is kept current as well [33]. Sites that can utilize the central IRBs have the advantage of a faster start-up time and therefore can usually start recruiting subjects earlier. Local IRB sites are responsible for submitting all documents to their IRB independently. This includes all modification and renewal documents as well. Studies will be required to submit a renewal submission prior to the expiration date every year. Most IRBs encourage submitting renewals 60–90 days in advance of the expiration date to ensure that the IRB has enough time to review any changes. At any point after the initial approval, a modification submission can be submitted for any changes in the proposed research. This includes (but is not limited to) changes to personnel, protocol amendments, new subject directed documents, or safety findings that may require updates to the informed consent documents. Consult your IRB coordinator or designated contact for clarifications on whether a required change needs to be submitted to the IRB. Usually, the answer is yes! Do not utilize new materials without submitting them to the IRB or confirming that they are IRB approved first.

2.6.6 Feasibility Continues with Budget and Contract Negotiations

The feasibility assessment does not end with the feasibility questionnaire and site selection. The successful investigator will be able to turn down a study that is not sufficiently funded. Before looking at the draft budget, the first step should be a methodical evaluation of the protocol, which should start with the schedule of assessments. Be sure to read the fine print found at the end of the schedule, which can clarify if certain procedures are required or only necessary under certain conditions. Special attention should be given to the procedures section of the protocol, which should clarify if personnel must have certain credentials to perform certain duties (i.e. efficacy assessments). The feasibility review can greatly impact the budget and scheduling constraints (e.g. Will the electrocardiogram (ECG) be reviewed by a cardiologist vs. another clinician?). Usually, these issues will be brought up at your site qualification visit, but some things get overlooked. Taking the extra time

to ensure that you have the appropriate patient population, staff, facilities, equipment, and expertise before you accept the proposal (i.e. sign on the dotted line) will help you avoid some of the most common errors that investigators make.

2.6.6.1 Budgeting

As with any budget, Industry-sponsored studies should be approached in an organized and methodical way. The contract negotiation process occurs at the same time as the budget negotiations and requires a keen eye and attention to details. A thorough review of the schedule of events can ensure that all procedure fees and assessments are being taken into account. From your feasibility assessment you know which staff members will be required to work on your study. Be sure to account for their time when conducting your budget review. Delineating PI/Sub-I time from SC time will allow you to better account for salary support. The schedule of assessments, the payment terms, and the draft budget should be reviewed together to ensure that all the line items match up. By developing a budget and payments checklist, you can be sure to account for all your costs. Do not just accept any payment terms. Pay attention to holdback percentage and final payment terms, monthly vs. quarterly payments, and screen failure terms. The difference can be in the details. Be sure to account for invoiced items like study start-up, IRB preparation for initial review, IRB amendment and renewal fees, document storage/archiving fees, and advertising costs. Some budgets may also require additional data entry fees, monitor visit fees, query resolution fees, and pharmacy fees. Be sure to take the extra time to evaluate the needs of each protocol. For particularly difficult-to-enroll studies, you may need to enlist the help of a recruitment coordinator and account for their time in the budget. You will have to ask yourself some hard questions here: Do you really have the time for this study? Can you afford to take this study given how much it may cost you in personnel time?

2.6.6.2 Contract and Payment Terms

Although not required, it is highly recommended that either a lawyer or someone with a legal background in corporate law review the contracts and payment terms. Institutional sites have a submission process for these documents to be reviewed by their legal department. For community practice sites, it is even more important for the PI to understand the terms of the agreement and be able to entrust someone who is trained on how to review and negotiate the terms.

2.6.6.3 Billing and Claims

It is becoming increasingly important for investigators to be up to date on the latest trends in regulatory and compliance matters. One such matter is conducting a Medicare coverage analysis to avoid unnecessary, and potentially very costly,

billing errors (i.e. false claims). This analysis determines routine costs which may be covered by Medicare or the patient's insurance vs. non-covered costs paid for by the study. This analysis is especially useful for studies that incorporate standard of care procedures/costs into the study. For many Industry-sponsored studies all the protocol-required procedures and assessments are covered by the sponsor and accounted for in the budget or contract, and therefore neither Medicare, the patient, nor their insurance should be billed. It should be clear from your review of the protocol, budget, and contract what all the potential costs are and who will pay for them.

2.7 Anti-kickback Statutes and Stark Law

Federal regulations strictly prohibit paying for or receiving inducements for patient referrals and further prohibit billing Medicare for services provided as a result of these referrals [34]. These laws are not limited to standard of care practices, but also extend to clinical research. Research subject referrals would also fall under the jurisdiction of these statutes. Therefore any kind of inducement or gift, whether monetary or other items of value, given or received for research subject referrals would also be prohibited. Research participants can, however, receive modest compensation for their participation in the study. The IRB/EC must approve compensation amounts to ensure that they are not coercive.

2.8 Working with CROs and SMOs

Working with a CRO or a site management organization (SMO) is standard practice in clinical research. With increasing regulations and tightening budgets, Sponsors (pharmaceutical companies) understand the importance of delegating the clinical research to groups with experience conducting and managing clinical trials. The CROs and SMOs are contracted to oversee and in some cases assume responsibility for certain duties as designated by the Sponsor or clinical investigator. These duties can include (but are not limited to) study management, negotiating contracts and budgets, site selection, data management, recruitment of study subjects, and evaluation of safety events (AEs and SAEs). Working with the middle man can inevitably cause delays in response times and the occupational hazard of working with a lot of people with very specialized roles. Generally, however, the standardization of the clinical research process across the industry tends to streamline the process. The same regulatory documents and general IRB submission processes are set in place for all studies. The difference is in the details and knowing the regulations (i.e. ICH GCPs and Code of Federal Regulations) [33, 35].

2.8.1 *Institutional/Academic Sites vs. Community Practice Sites*

Both institutional sites and community practice sites have their own advantages. Institutional sites can usually conduct studies with more intensive protocols (e.g. multiple blood draws over many hours, inpatient/overnight stays, specialized equipment/lab procedures). Some protocols require audiology, ophthalmologic testing, DEXA scans, specialized ELISA testing, or corneometry assessments. Institutional sites may be more likely to see rare or less common skin conditions (e.g. Hidradenitis Suppurativa and Epidermolysis Bullosa). Community sites, on the other hand, tend to have quicker start-up times, can utilize central IRBs, and the overhead/F&A costs at community sites tend to be lower than at Institutional sites. For high enrolling studies looking for subjects with more prevalent conditions (e.g. Psoriasis, acne, onychomycosis) community sites are more attractive.

2.9 Advantages of Training in Clinical Trials

There is a projected shortage of clinical trial investigators that has been attributed to several reasons [27, 36–38]:

1. Fewer medical students becoming M.D.-Ph.D.'s (physician scientists)
2. Decreased NIH funding
3. Lack of training in clinical research
4. Increased regulation and monitoring of clinical trials
5. Scarcity of mentors
6. Lack of adequate time for research

These factors are causing the pharmaceutical industries to look to private practices and sites outside the United States that can help them reach the goal of fast recruitment and enrollment. This could be a challenge but also an opportunity for physicians interested in becoming a PI. These are some of the advantages of becoming a clinical trials principal investigator (PI) [27, 39]:

Professional

- Allows you to remain on the cutting edge of a specific area of medicine
- Makes you knowledgeable of the new mechanisms of action, drugs available before anyone else
- Increases your professional recognition as an expert in the field
- Helps advance your academic career and promotions
- Adds prestige to your practice or institution
- Gives you the opportunity to meet, network, and collaborate with other experts in the field to promote new ideas
- Some PIs may be selected to contribute as co-authors for publications

Personal

- Personal satisfaction of giving more alternatives to your patients
- Seeing new drugs on the market that you helped get there
- Having a role in the advancement of medicine in your particular field
- Increased compensation

Patients

- Patients have early access to drugs that may be beneficial to them, increasing their options of treatment.
- Patients have the opportunity of receiving treatment at no cost for them, in a very controlled and safe environment.

Society

- The ultimate goal of clinical research is to benefit society by offering new information about the diseases or treatments.

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Useful Links

US Food and Drug Administration (FDA): www.fda.gov

Clinical Trials.gov: www.clinicaltrials.gov

Good Clinical Practices: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf

Association of Clinical Research Professionals (ACRP): www.acrpn.net

Society of Clinical Research Associates (SOCRA): <http://www.socra.org/>

Model Agreements & Guidelines international (MAGI): <http://www.magiworld.org>; http://magiworld.org/standards/MAGI_Model_CTA_Abbreviated.pdf

Example of a blank 1572 form: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf>

Training: <http://www.fda.gov/Training/default.htm>

Collaborative Institutional Training Initiative (CITI): <https://www.citiprogram.org/>

NIH Office of Extramural Research: <http://phrp.nihtraining.com/users/login.php>

Harvard Catalyst Master's Program in Clinical and Translational Investigation: <http://catalyst.harvard.edu/services/mpcti/>

NYU Langone Clinical and Translational Science Institute: <http://ctsi.med.nyu.edu/researcher-resources/training-and-education/degree-programs/msci/>

Food and Drug Administration Clinical Investigator Training Course: <http://www.fda.gov/Training/ClinicalInvestigatorTrainingCourse/default.htm>

Translational Biotechnology Fellowship at Galderma: <http://www.aad.org/education/awards-grants-and-scholarships/translational-biotechnology-fellowship>

Example of a Clinical Trial Agreement: <http://www.iom.edu/~media/Files/Activity%20Files/Research/DrugForum/April27-28/TemplateCTA%2042209.ashx>.

Clinical Dermatology Trials 101

A Primer for Dermatologists

Nasir, A. (Ed.)

2015, XX, 343 p. 65 illus., 59 illus. in color., Hardcover

ISBN: 978-3-319-09026-9