Back to Basics: How Foundational Training Can Save the Modern Clinical Trial

Summary

Running a successful clinical trial that generates high-quality data and finishes on schedule is the goal of every sponsor, but the increasing complexity and cost of clinical trials means that managing sites, ensuring protocol adherence, and enrolling the right patients can be a major roadblock. To address these challenges, it is essential that effective training be delivered to investigators, study coordinators, and other site staff, not just at study startup, but throughout the duration of the trial. Below, we discuss the shortcomings of traditional training models, the consequences of ineffective training, and how an audit-ready, standardized, and accessible approach to trial-related education can overcome those limitations.

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Reshaping the Face of Clinical Studies: A Trial by Fire

Clinical trials continue to evolve. New trial designs, biomarker identification techniques, digital technologies, decentralized formats, and advanced data analysis have facilitated the investigation of novel treatments for rare and heterogeneous diseases. Traditionally, trials relied heavily on geographical proximity to patients for enrollment, but hybrid and virtual formats have transformed this model. Enrollment, testing, data collection, and other procedures can now be done using telecommunications, cloud-enabled smart devices, and mail. Such advances in virtual trial support have helped to improve patient identification, recruitment, retention, and compliance. When the SARS-CoV-2 pandemic threatened to pause many clinical trials, these remote practices ensured that many could continue.

A Brief History of Clinical Trials

How did the scientific, ethical, and regulatory structure we use in modern clinical trials evolve? Here's a brief overview of the major milestones:[1]

1747 - James Lind performs the first controlled clinical trial with 12 scurvy patients and six treatment arms, one of which included 2 oranges and 1 lemon.

1946 - The first clinical trial of streptomycin's effect on pulmonary tuberculosis occurs, incorporating several breakthrough concepts in clinical testing such as randomization, enrollment criteria, and objective measures interpreted by experts who were blinded to each patient's treatment.

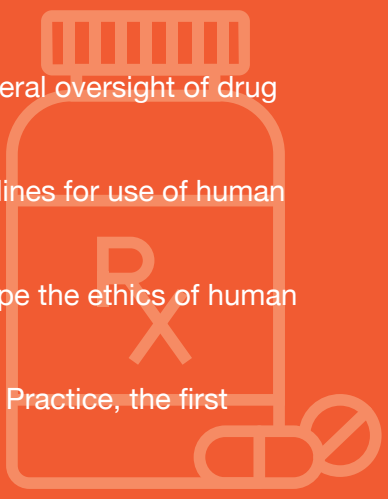
1947 - The first international ethical guidelines for clinical research, the Nuremberg Code, is formulated and makes informed consent an essential part of clinical research.

1962 - The U.S. passes the Kefauver-Harris amendments which strengthen federal oversight of drug testing and includes informed consent requirements.

1964 - The World Medical Association defines the general principles and guidelines for use of human subjects in medical research, the Helsinki Declaration.

1974 and 1979 - The U.S. National Research Act and Belmont Report help shape the ethics of human experimentation.

1996 - The International Conference on Harmonization publishes Good Clinical Practice, the first universal standard for the ethical conduct of clinical trials.



While new techniques, designs, and formats have advanced the conduct of clinical trials, they have also increased the complexity of initiating, managing, and concluding clinical trials in a timely manner.

Let's take a look at how clinical trials have (and continue to) change.

Operating at a Global Scale

The long-term goal of many clinical trial sponsors is to access drug approval in as many global markets as possible. In addition, many potential treatments are being investigated for diseases with small patient populations, requiring an expansion in the number of sites and regions contributing to studies to overcome slow rates of enrollment. To address these issues, clinical trials have grown in geographic scale and increasingly span multiple countries and continents. The payoff for doing this can be huge, but the logistics and effective management of running these distributed global trials is not straight forward. Different countries may require different trial characteristics (i.e., acceptable endpoints, comparator arms, etc.) for regulatory approval and emphasize different regulatory or ethical considerations.[2] In addition, providing training and risk-mitigation strategies across a range of sites whose staff speak different languages and have different cultural norms poses a challenge.

Complex Trial Designs Beget Complex Operations

Since the turn of the century, the number of distinct procedures performed during clinical trial visits and the total number of clinic visits required has increased across phase I, II, and III clinical trials (Figure 1).[3] In addition, the number of distinct endpoints targeted has increased by 86% and the total number of trial sites has increased by 63%.[4] Contributing to this trend is the growth in personalized medicine and companion diagnostics, which may require participant testing for specific genetic markers or biomarkers of pathology prior to enrollment. In addition, targeting rare and hard-to-treat diseases and the need to enroll increasingly stratified patient populations has also contributed to the increase clinical complexity.[4]

This complexity adds to the burden placed on site staff. There are more samples to collect, tests to perform, progressively complicated schedules of activities, and just more overall information that needs to be remembered and organized. This increased load, along with the rigors of regulatory compliance may in-part be causing the high turnover rate of Principal Investigators in clinical trials.[5] Complexity is also linked to a number of delaying factors for clinical trial timelines, including issues with mid-study protocol amendments, data quality, and patient retention.[3]

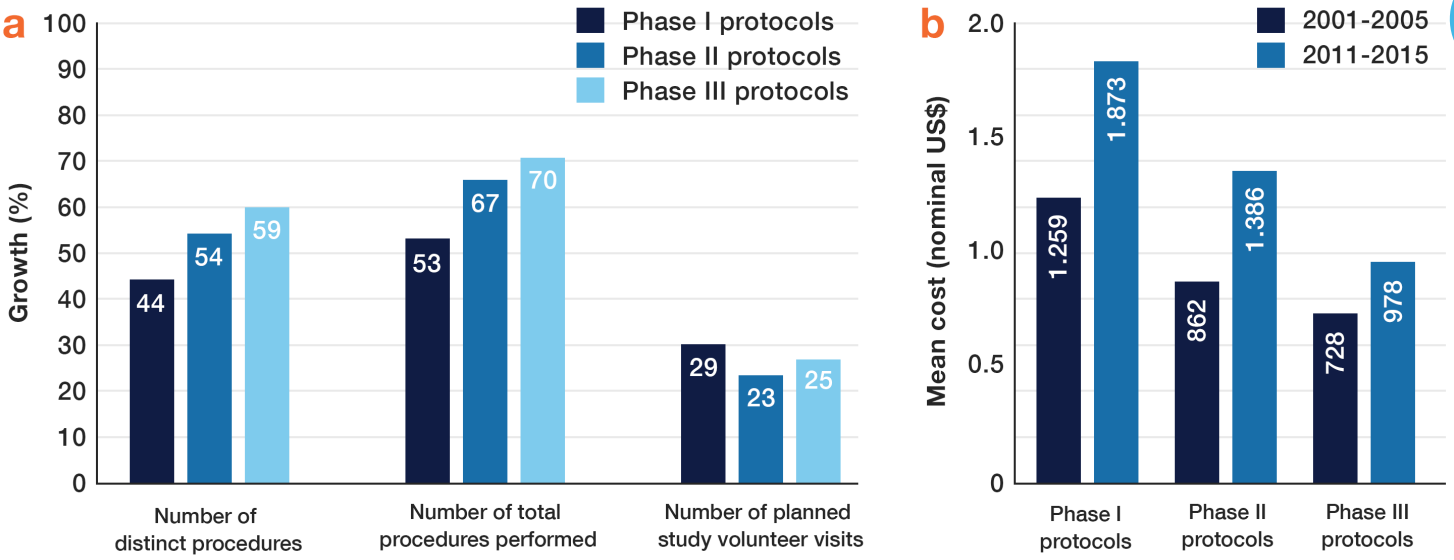


Figure 1. Growth in the clinical trial complexity and cost from 2011 to 2015, compared to 2001 to 2005. **a)** Percent growth in specific clinical trial characteristics across phase I, II, and III protocols from 2011 to 2015, compared to 2001 to 2005. **b)** Cost per volunteer visit across phase I, II, and III protocols from 2011 to 2015, compared to 2001 to 2005.[3]

"Protocol complexity [is linked to] longer cycle times, higher numbers of protocol amendments, and lower patient recruitment and retention rates."[3]

– Kenneth A. Getz & Rafael A. Campo

It All Comes Down to Cost

This growth in the scale and complexity of clinical trials has resulted in significantly greater total trial costs. Not surprisingly, reports show a significant increase in the cost per subject across all phases of clinical trials in just a ten-year span (Figure 1).[3] It's difficult to tease apart all of the factors contributing to these increased costs, but many are reflected in higher operational costs at the site level. Complex, large-scale trials may also take longer than anticipated to complete, leading to cost increases arising from sustained study operations. Protocol amendments, which can be more likely with complex trials, also contribute to higher costs; a major protocol amendment to a global study has a median cost of $141k.[9]

Breaking Down Clinical Trial Costs

What goes into the daily costs of running a clinical trial? Generally, drivers of trial costs include the cost of supplies and equipment, workforce, patient recruitment, study procedures and patient monitoring, study and data management, and regulatory compliance.

Let's look at a concrete example of a budget from a randomized, two-arm, phase III oncology clinical trial. The trial recruited 350 patients across 25 sites in the EU and the total duration was 66 months:[10]

Line Item	Total Cost
Regulatory affairs	$64,350
Site identification and selection	$46,200
Site contracting and payments	$64,350 (amounts paid per patient are listed as pass-through costs)
Site initiation and activation	$42,700
Site management	$950,400
Onsite monitoring	$1,069,670
Drug safety management	$29,820 (not including medical monitor)
Drug logistics	$55,790 (CRO cost not including depot subcontracted service)
Biological sample logistics	$74,620 (not including shipping costs, which are listed as pass-through costs)
Clinical supplies logistics	$22,575
Medical writing	$24,960
Site close-out	$40,950
Project management	$1,021,120
Study files/document management	$148,993
Data management	$435,851
Statistics	$150,518
Quality control	$70,460
Communication with central CRO/sponsor	$89,100
Pass-through costs	$8,526,728*
TOTAL	**$12,929,155**

*Pass-through costs are those expenses and services related to third parties and include, trial insurance policies for each country, shipping of samples, blood tubes and shipping packages, office supplies, payments to sites per enrolled patient (to cover clinical procedures and laboratory tests), publication fees, ethics committee evaluation fees, site contract fees, regulatory authority evaluation fees, travel costs for selection, initiation, routine monitoring, and close-out visits, central pathology and radiology reviews, translational/biomarker studies, coordinating investigators, drug manufacturing and testing, drug distribution services, EDC license and service fees, web tools (imaging platforms, eTMF), document translations, and Data and Safety Monitoring Board (DSMB).

This translates to a cost of nearly $200,000 per month to run this particular phase III study. While not all line-item costs are time sensitive, it's easy to see how increasing the length of a trial by several months impacts the bottom line.

Clinical Training and Education: The Cornerstone of a Successful Trial

In principle, many of the challenges posed by large-scale, complex clinical trials can be addressed by getting back to the basics: through efficient and consistent foundational education of site staff. Effective site training can ensure eligible patients are correctly identified, enrolled, and treated per protocol, without deviations. The quicker this happens, the quicker high-quality data can be collected and analyzed, and ultimately, the quicker a clinical trial can end. This can lead, in turn, to lower overall operating costs.

Of course, a lot of time, effort, and money are already dedicated to training site staff at investigator meetings (IMs) and site initiation visits (SIVs). Unfortunately, there are problems with the types of clinical training that have long been a mainstay in the industry – problems that can and need to be fixed.

Traditional Training through "Death by PowerPoint"

The use of presentation software like PowerPoint has dominated scientific and medical training for a long time. It is the preferred platform for presenting to medical and clinical audiences and in theory is a great tool for such a task. However, in practice it's infamously misused – to the point that "Death by PowerPoint" has come to be synonymous with the act of overwhelming an audience with dry slides packed with text, bullet points, tables, and figures. Unfortunately, it is a practice that all too commonly extends to IMs and SIVs.

This "information overload" is a common mistake made across many fields and levels of experience when training relies too heavily on traditional methods. And while sitting through these dense presentations may feel like "death" for many audience members, what it really amounts to is ineffective training. The leader of a training session may feel that they are communicating effectively because they are being comprehensive, but a deluge of information is sure to overwhelm the audience and ensure that only a small fraction of the content is absorbed. Poor presentation practices serve as a major obstacle to short-term learning, which is the gateway to long-term memory and the retention of knowledge.[11]

In addition to the misuse of presentation software, presentations are typically delivered at a pace set by the presenter, rather than having learning be self-directed by the audience. This can lead to missed information, with no mechanism to go back and review critical information that may have been missed.[12] While the same presentation format can be delivered virtually, making it useful when in-person training isn't possible, virtual presentations typically amplify many of the problems discussed above and remote audiences can be more easily distracted by any number of interruptions, like email or app notifications.

Problems at this foundational step of educating clinical trial staff can create a chain reaction of problems downstream.

Study Startup

During study startup, clinical teams are often trained at SIVs and other sessions on the disease state being investigated, the details of the investigational product, and the clinical trial protocol. It is particularly important that protocol training focus on high-risk areas related to eligibility and enrollment or the implementation of study procedures and assessments. Gaps in this initial training can lead to protocol deviations that increase data query rates, necessitate remedial training, and ultimately impact the quality of study data.

Retraining and Continuous Education

The goal for site staff is to ensure consistency and adherence to the protocol from the first patient enrolled to the last patient completed. But after initial training, that goal is threatened by the "forgetting curve," a natural loss over time of the information presented and learned during initial training. As we have seen, training that is less than optimal means a steeper rate of information loss. Compounding this loss of knowledge is the inevitable turnover that occurs in clinical trial staff as a trial continues. The burden of onboarding new staff mid-trial often falls to the most experienced members at a particular site, yet if they have already forgotten key parts of the protocol there is an all too real risk of perpetuating knowledge gaps or, worse, misinformation about the protocol. Further, new staff are often provided copies of material presented during study startup, which may have become outdated and can be challenging to absorb without accompanying explanation or active learning exercises.

Testing Comprehension

You don't know what you don't know. In clinical trial training, the best way to gauge the level of understanding of clinical trial staff knows is by performing pre- and post-training testing. While this may happen during study startup, few track the "forgetting curve" with ongoing knowledge assessments. Having an audit-ready record reflecting the current knowledge of your clinical trial staff can be challenging with traditional training methods.

Traditional training formats also make it more challenging to ask questions: site staff may be confused about something but could be less likely to pose their question in front of their peers for fear of looking unknowledgeable. This can lead to the perpetuation of knowledge gaps among site staff.

Training at Global Sites

Given the number of clinical sites across the globe participating in any given clinical trial, with traditional training methods there is no way to ensure complete standardization of site staff training. Across sites, presenters may vary in the elements they choose to emphasize or may simply be better or worse speakers. This leaves a lot of training to chance and creates a lack of consistency across sites. And the worse the training, the higher potential for downstream consequences.

Finding Life After Death by PowerPoint

There are now many ways to avoid "Death by PowerPoint", but an improved understanding of best practices in medical education is needed. Traditional presentation tools can be used to much greater effect when paired with newer methods to ensure that IMs, SIVs, and follow-on training sessions communicate the most important information to clinical audiences and that these audiences retain that information so it is put into practice. Simply checking the training box is no longer an option.

Online, virtual learning options, often called e-learning, afford a lot of potential benefits that aren't possible with tools like PowerPoint.[12] The most common way in which e-learning is delivered uses modules to break down complex topics and concepts into easily-digestible bits of multimedia content with a voiceover narration. Many site staff prefer this method of learning and research studies have found that, when used correctly, virtual learning is equally if not more effective than traditional in-person training.[12,13] Some of the benefits of this type of clinical training include:[13,14]

- **Ability to use different types of multimedia, catering to a variety of learning styles**
- **Complex content can be broken down into small, easily digestible modules**
- **Easy pre- and post-training knowledge assessment that can be analyzed to guide training modifications or captured to support external training audits**
- **Can be completed or revisited at the convenience of site staff**
- **Adaptable for use with live and virtual meetings**
- **Standardized delivery of training content across all sites and staff**
- **Easy to update or add module for protocol amendments**
- **Can complement in-person training (i.e., onboarding of new team members)**

SMi Trial: The E-Learning Solution to Keep Your Trial Deviation-Free and On Time

SMi Trial is a unique e-learning platform from ScienceMedia where content is customized to address the highest risk areas of your trial, ensuring that site staff are trained effectively over the duration of the study. The mobile-enabled platform delivers engaging multimedia training whenever and wherever you need it. Beyond initial study training, SMi Trial can also disseminate standardized supplemental training for protocol amendments or other targets, all while providing real-time, audit-ready analytics on therapeutic and protocol knowledge.

All of this means that clinical staff are operating at their highest level of competency and collecting the highest quality data possible.

Visit **sciencemedia.com/trial** to see how SMi Trial can help prevent protocol deviations, improve the quality of clinical data, resulting in decreased operational costs and deviation rates, ultimately expediting your time-to-market.

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