An Executive Summary

Three Necessary Steps When Designing your New World Protocol

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Putting patients first and simplifying their experiences with well-chosen decentralized techniques promises to improve clinical trials for everyone.

Overview

This article explores the design of a protocol that includes decentralized components. After a clinical-trial protocol has been developed, adding decentralized components—such as wearable devices for data collection or telemedicine visits—gets complicated. It is significantly easier to incorporate decentralized elements while designing the protocol, similar to how wiring a house during construction is easier than wiring post-construction.

Analyzing the Old World

In a webinar hosted by *Applied Clinical Trials* and *Pharmaceutical Executive* and sponsored by Oracle Health Sciences titled "Three Necessary Steps When Designing your New World Protocol," the audience provided information on their organizations' use of decentralized trials in the past 12 months. The results showed that 37.5% of the participants responded, "never been in use in our organization." This poll showed that about one-third of respondents use the old-world protocol, which can be summarized as an approach to clinical trials used over nearly the past century that has remained mostly unchanged. The Federal Food, Drug, and Cosmetic Act of 1938 determined the method used in this era of clinical trials. Thus, the evolution of clinical trials has not kept pace with advances in related fields, such as genomics and medicine.

In the first and accidental clinical trial, described in the Bible's Book of Daniel, King Nebuchadnezzar of Babylon ordered his people to eat only meat and drink only wine in hopes of improving their health. Some of the people, though, ate a vegetarian diet and drank only water. In terms of health, the vegetarians fared better than the meat-eaters. Despite the obvious problems with this example as a clinical trial—and it is being used in a light-hearted way—the King's proclamation serves as an early, old-world example of comparing groups for health outcomes.

For a more modern look at clinical trials, consider **Figure 1**. This illustration documents the basic flow of clinical research despite a wide variety of clinical trials, patient populations, and so on. The lifecycle goes from an approved protocol to filing data and obtaining registration for a treatment. Although this represents the past (and largely current) approach to running clinical trials, it fails to take advantage of existing technology and stakeholders, especially the key ones, which are the patients and participants.

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Figure 1: Current clinical research paradigm: Clinical trial lifestyle.

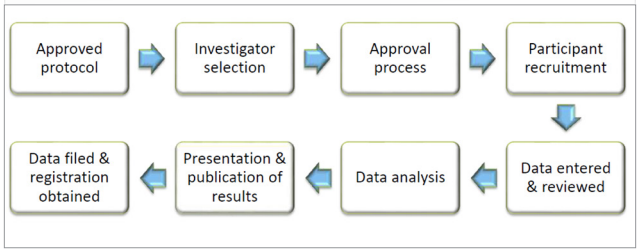
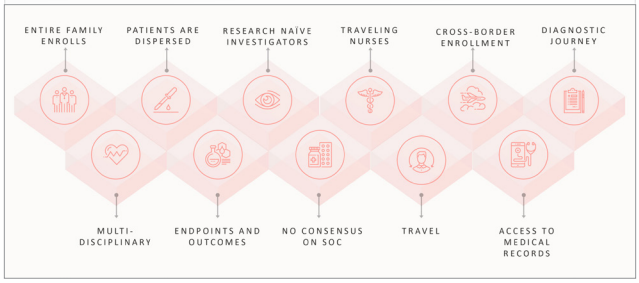


Figure 2: Why clinical trials should be focused on the patient.



This flow includes several weak points that start with developing the protocol in a vacuum, which prevents input from people at clinical sites and patients. The process may also include many endpoints, time points, and assessments that are not realistic. For example, a protocol could expect patients to travel to a clinical site every week for six months or get a high number of blood draws. Such expectations may not fit into the lives of the patients.

The old-world design may not even ensure that the required patients exist because of more than a dozen criteria for eligibility, inclusion, and exclusion that could be used. Even if the needed patients exist, the designed trial may not appeal to enough of them. Although patients do not pay to participate in a trial, costs accrued through travel, time off work, childcare, and so on should be considered.

Combining all of the patient challenges depicts the overall burden. Nonetheless, the designers of a clinical-trial protocol often fail to even consider the patient perspective.

Putting Patients First

As shown in **Figure 2**, a clinical trial should put patients first for many reasons. In many cases, especially with children or elderly patients, an entire family must be involved even when only one person is enrolling in a trial. Geographic dispersal and many other factors might also impact who can participate. These patients decide if they want to participate in a trial, and that gives them more power in driving clinical research.

In the previously mentioned webinar, the audience responded to the schedule of evaluations for a relatively ordinary old-world protocol. About two-thirds of the participants called the evaluation about the usual, but 23% labeled it as awkward, and nearly 14% called it wrong.

To make patients feel first in the process of designing a clinical trial, the designers must think about these end users. This makes the patient perspective a key element in trial design and requires asking patients about trial experiences. In a survey conducted after a trial that asked patients about challenges associated with the trial, travel topped the list, and time commitment came in second. At lesser frequencies, patients also noted the financial strain, family strain, invasive procedures, cultural barriers, and side effects as other notable challenges. With so many clinical trials delayed because of problems in enrollment and clinical development, this shows the need for patient input.

In one survey of patients who did not participate in a trial, the number one reason was not meeting the eligibility criteria. Secondly, patients found that enrollment was over, as some designs do include a short enrollment window. In other cases, patients did not participate because a trial was too far away, not offered, or because of an array of other reasons ranging from fear to finances.

To see what is needed to decentralize a trial, the webinar audience was asked, "What do you or your team need more of to be more effective and successful with incorporating decentralized components in trials?" In the pool, 29% picked knowledge, 34% needed more technologies, 18.5% needed more resources, and 16% required more skills training.

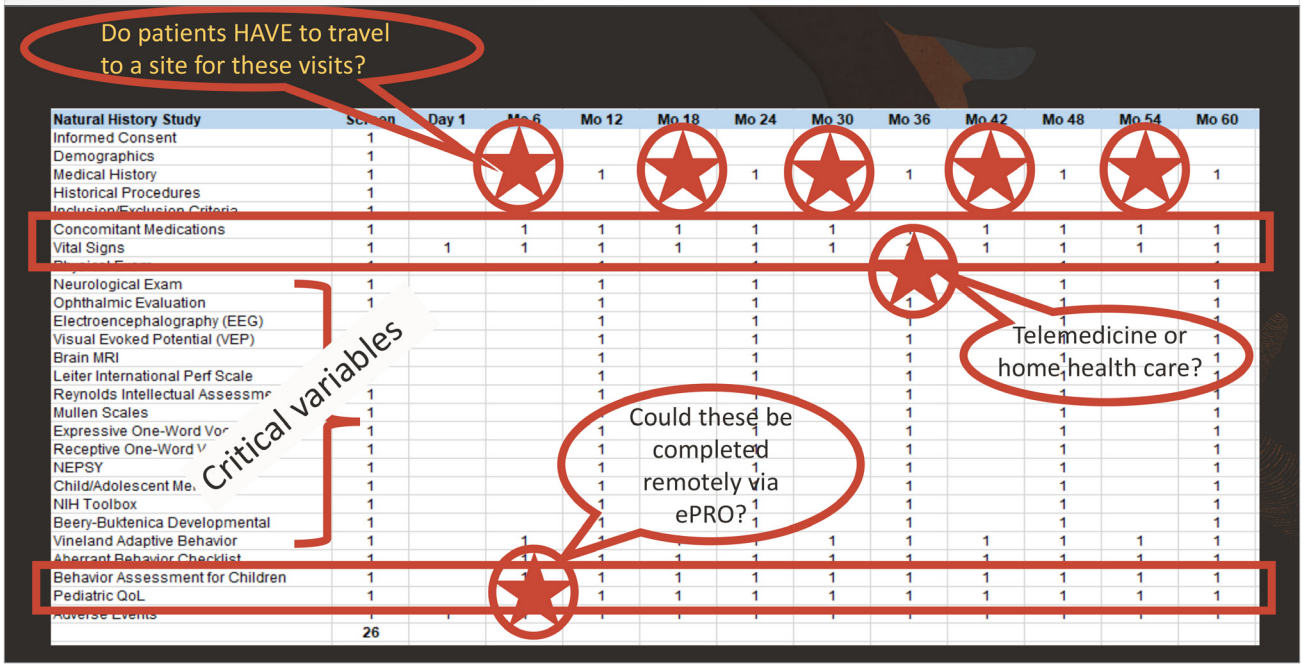
Whatever elements a clinical-trial designer needs to add decentralized components to, they do not need to be done all at once. Instead of jumping completely from an old-world approach to something entirely different, a designer could simply add one or two improvements, such as reducing the number of visits for patients or using technology to simplify a patient's experience.

A New World Approach

From previous webinars in this series, audience polls showed that patient convenience ranked as a top reason to incorporate decentralized elements in clinical trials. Other top reasons included patient engagement and retention. Some members of those audiences also mentioned improving data quality.

As noted above, protocols often assume the existence of the needed patient population. In a dataset for a patient population and a specific disease state, 60% of the patients were under the age of 18 and could not enroll in a trial on their own. These patients averaged 2.2 hospital visits a year, but a clinical trial would require many more visits, which could be especially taxing when the whole family could be involved with patients who are minors. If deemed too inconvenient, patients will not participate.

Figure 3: Data from a natural history study.



Natural History Study	Screen	Day 1	Mo 6	Mo 12	Mo 18	Mo 24	Mo 30	Mo 36	Mo 42	Mo 48	Mo 54	Mo 60
Informed Consent	1											
Demographics	1											
Medical History	1			1		1		1		1		1
Historical Procedures	1											
Inclusion/Exclusion Criteria	1											
Concomitant Medications	1		1	1	1	1	1	1	1	1	1	1
Vital Signs	1	1	1	1	1	1	1	1	1	1	1	1
Physical Exam	1											
Neurological Exam	1			1		1				1		1
Ophthalmic Evaluation	1			1		1		1		1		1
Electroencephalography (EEG)				1		1		1		1		1
Visual Evoked Potential (VEP)				1		1		1		1		1
Brain MRI				1		1		1		1		1
Leiter International Perf Scale				1		1		1		1		1
Reynolds Intellectual Assessme	1			1		1		1		1		1
Mullen Scales	1			1		1		1		1		1
Expressive One-Word Voc	1			1		1		1		1		1
Receptive One-Word V	1			1		1		1		1		1
NEPSY	1			1		1		1		1		1
Child/Adolescent Me	1			1		1		1		1		1
NIH Toolbox	1			1		1		1		1		1
Beery-Buktenica Developmental	1			1		1		1		1		1
Vineland Adaptive Behavior	1		1	1		1	1	1	1	1	1	1
Aberrant Behavior Checklist	1		1	1	1	1	1	1	1	1	1	1
Behavior Assessment for Children	1		1	1	1	1	1	1	1	1	1	1
Pediatric QoL	1		1	1	1	1	1	1	1	1	1	1
Adverse Events	1	1	1	1	1	1	1	1	1	1	1	1
	26											

In the schedule of evaluations mentioned previously, clinical visits for concomitant medications and vital signs, for example, could be accomplished with telemedicine or home-health visits to reduce a patient's burden. Some assessments, such as quality of life, could be done electronically from home. Still, some critical variables, including EEGS and brain MRIs, require a site visit.

Items starred in **Figure 3** could be considered for elimination, or as places to simplify a patient's experience. This natural history study is non-interventional and lasts for months, which makes it as easy of a study as there is. However, it is important to note that the schedule would probably triple in complexity for an intravenous treatment for a rare cancer tumor. In all cases, opportunities exist to eliminate some visits or to leverage some technology.

Organizational Opportunities

Some people probably wonder if their organization can make changes in clinical-trial design. Keep in mind that many industries are changing. For instance, the world's largest hotelier, Airbnb, owns no hotel rooms, and the world's largest taxi companies, Uber and Lyft, own no taxies. The clinical-trial industry could change by starting to think of patients a little more like consumers or customers.

At the Summit for Clinical Ops Executives (SCOPE) in Orlando in February 2020, a snap poll was conducted with people involved in protocol development. Only 7% of the participants responded that they always do research to incorporate the new and best approaches in this area. Still, the results show that people who stayed informed about new methods do incorporate them in protocols, but many opportunities remain.

Conclusion

The first step in designing a new world protocol depends on making the patient a key player in the process, which entails collecting feedback from patients after trials and involving patients in the design of upcoming trials. Simplifying the process and overall experience for patients are worth-while objectives for improving clinical trials. This can be done with simplifying some steps, such as eliminating unnecessary visits or replacing unnecessary visits with decentralized tools, such as wearable data-collection devices or telemedicine. Though most trials will still require some site visits, adding decentralizing elements in smaller steps can keep the overall process simple yet efficient.

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