How Modern Science Changed the Shape of Clinical Trials

Understanding movement, control, and supply reality in modern study execution

Knowledge Sharing Series

4G CLINICAL

How Modern Science Changed the Shape of Clinical Trials

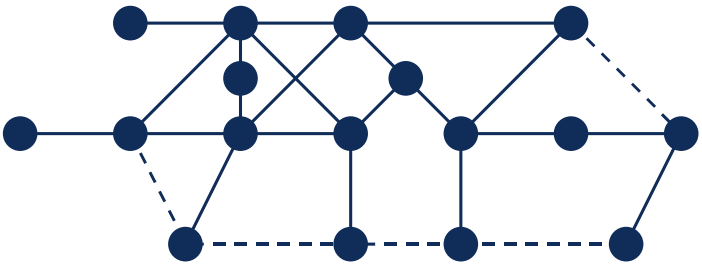
Introduction: Complexity has a scientific source

Trial complexity is not the enemy. It is often the consequence of better science.

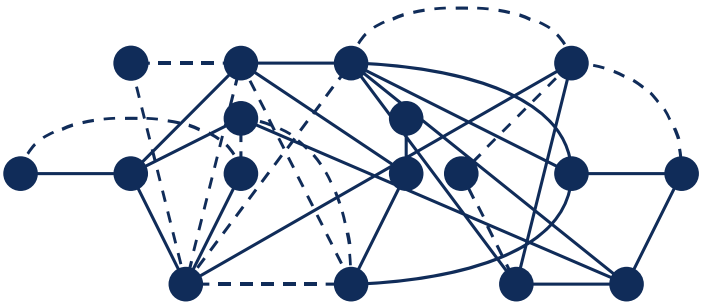
That is an important place to begin. Clinical trial complexity is usually discussed as an operational problem: longer protocols, more countries, more vendors, more amendments, more data, more systems, more supply pressure, more work for sites. All of that can be true. But it is not the entire story.

Not all complexity is valuable. Some complexity is created by unclear processes, fragmented systems, unnecessary manual work, or late interpretation of protocol requirements. That kind of complexity should be reduced. But some complexity exists because the science is doing more: selecting patients more precisely, learning from accumulating data, adapting treatment pathways, or managing supply around narrower populations. The challenge is knowing the difference.

Valuable Complexity



Unnecessary Complexity



Many of the things that make modern trials harder to run also reflect progress in how research is designed. Medicine has become more targeted. Early-phase studies have become more deliberate about dose learning. Adaptive and platform designs have created ways to answer more than one question over time. Biomarkers have made it possible to think more carefully about which patients may benefit. Patient access models and supply strategies have had to become more responsive to real-world disruption.

As patient populations narrow, cohorts move, dose decisions change, and countries activate unevenly, supply planning becomes part of the scientific operating model rather than a downstream logistics exercise.

In other words, modern trials are not more complex simply because the industry made them complicated. They are more complex because the questions have become more precise.

Earlier studies were often built around more contained questions. Does this treatment work compared with an alternative? Is this dose tolerated? Does this intervention improve an outcome in a defined population? Those questions still matter, but many modern studies ask something more specific. Which patients should enter? Which biology matters? Which dose should move forward? Which cohort should expand? Which treatment arm should continue? Which supply plan still reflects the study as it is actually behaving?

That is progress. It is also operationally demanding.

The challenge is not to make the science simpler. The challenge is to understand what the science is asking the study to do, where that creates movement, and what must remain controlled as the study changes.

That is the premise of this paper. To let the science lead, the operating model has to be able to follow.

A brief history of controlled movement

Clinical trials did not become complex all at once. The changes accumulated over time as researchers found better ways to protect evidence, learn from patients, and match trial design to the questions medicine was trying to answer.

1946-1948
Randomization needed control

1989
Dosemovement needed structure

2005
Adaptive trials made movement part of the model

2009-2011
Biology began shaping eligibility, assignment,and pathways

2020
Supplyplanning had to respond to live trial reality

A brief history of controlled movement *(continued)*

One useful starting point is the Medical Research Council's streptomycin trial in pulmonary tuberculosis, planned in 1946 and published in 1948. The trial is widely recognized as a landmark in the development of modern randomized clinical trial methodology because of its use of random allocation and the steps taken to prevent foreknowledge of treatment assignment (Chalmers, 2011; Medical Research Council, 1948).

The lesson was not only statistical. It was operational. Evidence needed trust, and trust depended on protecting the method of assignment. If investigators could predict or influence which treatment a patient would receive, the comparison between treatment groups could be affected before treatment was ever given. Randomization helped separate treatment assignment from human influence. Concealment helped protect the moment of enrollment.

That principle still sits underneath clinical trial execution. Randomization was never just a list. It was a control point designed to protect the comparison being made. In modern trials, that control point may now be connected to stratification, blinding, cohort status, biomarker information, treatment availability, kit assignment, dispensing, inventory, reporting, and downstream data flows. The original need remains, but the number of dependencies around that need has expanded Early-phase oncology added another kind of movement. Before a treatment can move into broader testing, a study often has to decide how much can be given, what can be tolerated, and when the next dose decision should occur. Storer's 1989 paper on Phase I trial design is one historical reference point for dose-escalation methods and maximum tolerated dose estimation (Storer, 1989).

The traditional 3+3 design became familiar because it gave early studies a structured way to move through uncertainty. The point is not that 3+3 is the ideal model for modern development. It is that dose movement needed rules. A study could not simply escalate because someone felt ready to escalate. It needed defined conditions for moving, pausing, expanding, or stopping.

Modern escalation and expansion studies may include backfill, titration, de-escalation, multiple schedules, combination therapy, dose optimization, and population-specific rules. The operating model is broader now, but the underlying lesson remains. Dose movement carries risk, so it needs structure.

Adaptive and platform trials changed the shape again. STAMPEDE, a multi-arm, multi-stage platform trial in prostate cancer that opened in 2005, was designed to test several treatment approaches within one ongoing trial structure (James et al., 2008). Later STAMPEDE work described the practical issues involved in stopping arms for lack of benefit and adding research arms mid-trial (Sydes et al., 2012).

STAMPEDE is useful because it shows that movement can be part of the trial model from the beginning. Arms could stop, continue, or be added as evidence developed. That was not flexibility in a loose sense. It was controlled adaptation. The trial needed rules for what could change, when decisions could be made, how those decisions were documented, and how the current approved version of the study was reflected in practice.

A brief history of controlled movement *(continued)*

Biology then began to shape trial design more directly. BATTLE-1, the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination trial, is a strong example. It has been described as a prospective, biopsy-mandated, biomarker-based, adaptively randomized Phase II trial in previously treated non-small cell lung cancer, using tumor profiling and real-time biomarker analysis to help guide treatment assignment (Kim et al., 2011; Liu et al., 2015).

The important shift is that biology did not sit outside the study. It helped determine how patients moved through it. Biomarker information could affect eligibility, cohort entry, treatment assignment, and demand. That made the trial more scientifically specific but also more dependent on whether those scientific rules could be reflected clearly during conduct.

The 2020 pandemic made another kind of movement visible: supply movement. Direct-to-patient models were not invented during COVID-19, but the pandemic accelerated the need to think differently about how investigational products could reach participants when standard site-based assumptions were disrupted. European COVID-19 clinical trial guidance addressed direct shipment of investigational medicinal products to trial participants under defined conditions, including considerations around home storage, transit stability, accountability, compliance, and temperature control (European Commission et al., 2022).

The larger lesson was not only about direct-to-patient. It was that clinical supply planning has to respond when the study behaves differently than expected. Supply assumptions are shaped by enrollment, country activation, cohort movement, dose changes, expiry, depot strategy, and patient access. When those inputs shift, the supply plan has to be close enough to the live study to shift with them. Later research on direct-to-participant investigational medicinal product supply in Europe identified several models and highlighted practical, regulatory, and oversight considerations (de Jong et al., 2023).

Together, these moments show a pattern. Clinical trials became more controlled, more structured, more adaptive, more biologically specific, and more responsive to live operational reality. Each step improved the science. Each also changed what execution had to support.

When scientific complexity becomes execution complexity

Scientific complexity becomes execution complexity when it changes what the study has to do.

A biomarker requirement is not only a scientific feature if it determines whether a patient can enter a cohort, receive a treatment, or move forward in the study. A dose decision is not only a clinical judgment if it changes which dose levels are open, which patients can enroll, what can be dispensed, or what supply is required. An adaptive design is not only a statistical approach if the current version of the study has to be reflected across sites, systems, reports, inventory, and audit trails.
This is the point where modern trial design becomes operational.

The scientific requirement may be clear in the protocol, but the study still has to decide how that requirement behaves during conduct. What must happen before a patient can be assigned? What information has to be available before treatment can be dispensed? What changes when a cohort pauses, an arm closes, a dose expands, or a biomarker-defined group enrolls faster than expected?

These are not separate operational details. They are the way the science becomes executable.

This is also where avoidable complexity can enter the study. If the scientific requirement is not translated clearly, teams may rely on manual checks, site-level interpretation, duplicate data entry, spreadsheets, email instructions, or late-stage system updates. Those workarounds may keep the study moving in the short term, but they can create inconsistency, delay, and additional burden.

The goal is not to remove the complexity required by the science. The goal is to reduce the complexity created by unclear execution.

That distinction matters. A targeted study may need biomarker-driven pathways. An early-phase oncology study may need dose movement. A platform trial may need arms that can stop, continue, or be added. A constrained supply model may need planning that responds to live demand. Those requirements are not the problem. The problem appears when the operating model does not make those requirements clear, controlled, and usable.

Modern trials are shaped by dependencies

The easiest mistake is to describe modern trial complexity as if it were simply more of everything: more visits, more vendors, more countries, more systems, more amendments. That may be accurate, but it does not teach much.

*A more useful way to understand modern trial complexity is through **dependencies**.*

A biomarker result is not just a laboratory result if it determines whether a patient can enter a cohort. A cohort decision is not just a clinical decision if it changes what treatment can be assigned. Treatment assignment is not just a randomization event if it triggers dispensing, kit selection, inventory movement, and reporting. A dose decision is not just a safety decision if it changes cohort status, titration rules, supply demand, and amendment planning. A supply forecast is not useful if it still reflects assumptions after the study has already moved.

For supply teams, this is where complexity becomes very practical. A study may have enough product globally and still face a risk at the patient level if inventory is in the wrong country, held at the wrong site, nearing expiry, or aligned to a cohort that is no longer enrolling as expected. Supply risk is not only total quantity. It is timing, location, usability, and alignment with the current study design.

This is where modern trials become difficult to run. The challenge is not only that there are more moving parts. The challenge is that the moving parts affect one another.

A patient pathway may depend on testing. Testing may determine cohort entry. Cohort entry may affect assignment. Assignment may affect dispensing. Dispensing affects inventory. Inventory affects resupply. Resupply affects continuity. A protocol amendment may affect all of it.

When those connections are understood early, complexity can be managed with more discipline. When they are discovered late, teams often have to rely on workarounds, manual reconciliation, urgent amendments, or system changes that carry more operational pressure than they needed to.

When dependencies are not translated clearly, the burden often lands at the site. A coordinator may be asked to determine whether a patient can move forward, whether a cohort is open, whether a biomarker result is sufficient, whether a dose is available, or whether a dispensing action is allowed. That is not where ambiguity should live. The more sophisticated the science, the more important it becomes to keep site workflows clear.

This is why “flexibility” by itself is not enough. A flexible process that does not protect the rules of the study can create risk. A rigid process that cannot reflect expected movement can create delay. The goal is neither flexibility for its own sake nor control for its own sake. The goal is to understand where the study is expected to move and where control must hold.

That distinction matters. Modern science often creates movement, but movement is not the same as disorder. A trial can be adaptive and still disciplined. It can be targeted and still executable. It can be supply-conscious and still protect patient continuity. The work is to know what can change, what cannot change, and what has to stay aligned when change occurs.

The protocol is the scientific intent, not the full operating map

The protocol remains the center of the study. It defines the scientific question, patient population, eligibility rules, treatment design, visit schedule, endpoints, and safety requirements. It is the source of intent.

But the protocol is not always written as an operating map.

A protocol may state that assignment depends on biomarker status, but the operating model still has to define when the result is required, what happens if it is delayed or inconclusive, how the cohort is controlled, and how treatment demand should be planned. A protocol may define dose escalation criteria, but the study still has to determine how cohort status changes, how sites know what is open, how dispensing rules update, and what supply is needed if a dose expands. A protocol may describe adaptive movement, but the live study still has to keep assignment, dispensing, inventory, reporting, and audit trail aligned to the approved version of the design.

This is where execution often becomes difficult. The protocol can be scientifically clear and still leave operational dependencies that have to be interpreted, designed, tested, governed, and supported.

That is not a criticism of the protocol. It is a recognition of what a protocol is and what it is not. The protocol tells the study what it is trying to do. The operating model has to make sure the study can actually do it.

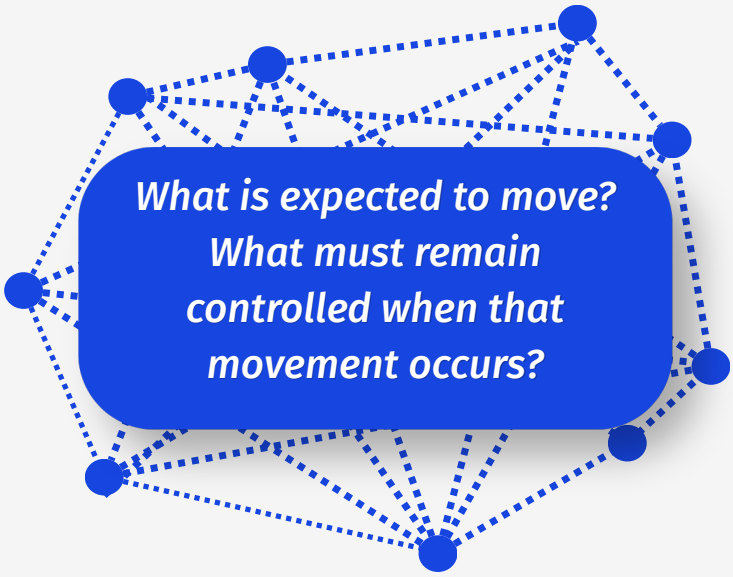
This is especially important when the science is expected to move. Footnotes, visit tables, escalation rules, cohort language, biomarker requirements, regional differences, drug supply assumptions, and amendment pathways can all become execution-critical. A detail that looks small in the protocol can become significant when it determines what a site can do, what treatment a patient can receive, or what supply has to be available.

Reading the protocol is the beginning. Understanding how the protocol behaves in the live study is the work.

What moves, and what must remain controlled?

A useful way to approach modern trial execution is to ask two questions early. The first is what is expected to move? In some studies, the answer may be dose levels. In others, it may be cohorts, treatment arms, biomarker-defined groups, country participation, site activation, enrollment patterns, supply demand, patient pathways, visit schedules, or amendment requirements. The point is not to predict every future change perfectly. The point is to identify the parts of the study most likely to create operational movement.

The second question is what must remain controlled when that movement occurs. This is where the study's operational discipline becomes visible. Randomization integrity must hold. The blind must be protected. Eligibility rules must be applied consistently. Treatment availability must reflect the approved design. Dispensing logic must match assignment rules. Inventory visibility must support supply decisions. Reports must show the current study state. An audit trail must preserve what changed, when, and why.



Patient dosing continuity must remain protected.

These questions are practical because they force the team to think beyond the launch version of the study. A launch design may be accurate on day one and incomplete by month six if the study is designed to learn, adapt, expand, or respond to live supply conditions.

The strongest operating models do not try to remove all complexity. They make clear which complexity is required by the science, where it will appear, and how it will be controlled.

A practical lens: what the study will need to do

The operating shape of a study is not always obvious from the protocol alone. It becomes clearer when teams look at where scientific requirements create decisions, dependencies, and movement.

For...	The Question is...
Patient Pathways	What determines whether a patient can move forward?
Dose and Cohort Movement	Which pathways may open, pause, close, expand, or backfill?
Assignment and Dispensing	What must be true before treatment can be assigned or dispensed?
Supply Behavior	What could make demand appear somewhere different from the original plan
Change Control	What must be updated together when the study changes?

These questions are useful because they move planning beyond the launch state of the study. They help teams see where the science is likely to create movement and where the operating model needs to maintain control.

When the operating model has to follow the science

When science changes the shape of the trial, the systems and processes used during conduct have to reflect that shape. This is not only a technology question. It is a design, interpretation, governance, and support question.

For many studies, the challenge is making sure the current approved version of the design is reflected consistently where people actually work. Sites need to know which patients can move forward. Study teams need visibility into cohort, dose, arm, and supply activity. Supply teams need planning assumptions that reflect live study behavior. Reports need to show the current state of the study. Changes need to be traceable.

RTSM is one of the technologies that can support this alignment because it often sits close to patient assignment, dispensing, inventory, resupply, reporting, and live study change. It is not the science. It should not define the study. But it can help ensure that important parts of the study design are reflected in the workflows and controls used during conduct.

For supply teams, that proximity matters because randomization, dispensing, cohort status, enrollment behavior, and inventory activity are often the signals that reveal whether the original supply plan still matches the live study.

The value comes from how well the protocol has been interpreted, how clearly expected movement has been anticipated, and how carefully change is governed once the study is live. A system cannot compensate for poor understanding of the protocol. It can, however, support a well-understood operating model by helping keep assignment logic, treatment availability, dispensing rules, inventory visibility, reporting, and traceability aligned as the study changes.

This is the practical role technology should play. It should not force the science into a simpler shape. It should help the study operate according to the shape the science requires.

Let the Science Lead

Modern trial complexity should not be treated as something to flatten. Much of it exists because clinical research is asking better questions.

*Which patients are most likely to **benefit**?*

*Which dose should move **forward**?*

*Which cohort should **expand**?*

*Which arm should **continue**?*

*Which treatment should **match which biology**?*

*Which supply plan reflects the study as it is **actually behaving**?*

These are better questions than clinical research could ask in earlier eras. They deserve operating models that can follow them.

Letting the science lead means respecting the study design rather than forcing it into a simpler shape for the convenience of systems or processes. It also means recognizing that scientific progress creates operational responsibility. If the trial moves, the controls must move with it. If the patient pathway depends on biology, the workflow has to reflect that. If supply demand changes with enrollment, dose, cohort, or country activity, the plan has to follow the study.

Trial complexity is not the enemy. It is often the consequence of better science. The work is to understand where that science creates movement, what must remain controlled, and how to keep the study executable as it evolves.

References

Chalmers, I. (2011). Why the 1948 MRC trial of streptomycin used treatment allocation based on random numbers. Journal of the Royal Society of Medicine, 104(9), 383-386. https://doi.org/10.1258/jrsm.2011.11k023

de Jong, A. J., Santa-Ana-Tellez, Y., Zuidgeest, M. G. P., et al. (2023). Direct-to-participant investigational medicinal product supply in clinical trials in Europe: Exploring the experiences of sponsors, site staff and couriers. British Journal of Clinical Pharmacology, 89(12), 3512-3522. https://doi.org/10.1111/bcp.15850

European Commission, European Medicines Agency, & Heads of Medicines Agencies. (2022). Guidance on the management of clinical trials during the COVID-19 pandemic, version 5.

James, N. D., Sydes, M. R., Clarke, N. W., Mason, M. D., Dearnaley, D. P., Anderson, J., Popert, R. J., Sanders, K., Morgan, R. C., Stansfeld, J., Dwyer, J., Masters, J., & Parmar, M. K. B. (2008). STAMPEDE: Systemic therapy for advancing or metastatic prostate cancer: A multi-arm multi-stage randomised controlled trial. Clinical Oncology, 20(8), 577-581. https://doi.org/10.1016/j.clon.2008.07.002

Kim, E. S., Herbst, R. S., Wistuba, I. I., Lee, J. J., Blumenschein, G. R., Jr., Tsao, A., Stewart, D. J., Hicks, M. E., Erasmus, J., Gupta, S., Alden, C. M., Liu, S., Tang, X., Khuri, F. R., Tran, H. T., Johnson, B. E., Heymach, J. V., Mao, L., Fossella, F., Kies, M. S., … Hong, W. K. (2011). The BATTLE trial: Personalizing therapy for lung cancer. Cancer Discovery, 1(1), 44-53. https://doi.org/10.1158/2159-8274.CD-10-0010

Liu, S., Lee, J. J., Wistuba, I. I., Tannir, N. M., Kantarjian, H. M., & Kurzrock, R. (2015). An overview of the design and conduct of the BATTLE trials. Chinese Clinical Oncology, 4(3), 33. https://doi.org/10.3978/j.issn.2304-3865.2015.05.04

Medical Research Council. (1948). Streptomycin treatment of pulmonary tuberculosis: A Medical Research Council investigation. British Medical Journal, 2(4582), 769-782.
Storer, B. E. (1989). Design and analysis of phase I clinical trials. Biometrics, 45(3), 925-937. https://doi.org/10.2307/2531693

Sydes, M. R., Parmar, M. K. B., Mason, M. D., Clarke, N. W., Amos, C., Anderson, J., de Bono, J., Dearnaley, D. P., Dwyer, J., Green, C., Jovic, G., Ritchie, A. W. S., Russell, J. M., Sanders, K., Thalmann, G., & James, N. D. (2012). Flexible trial design in practice: Stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: A multi-arm multi-stage randomised controlled trial. Trials, 13, 168. https://doi.org/10.1186/1745-6215-13-168

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