Clinical trial protocols are designed to produce scientifically sound, new knowledge about the safety, efficacy, and specific therapeutic characteristics of a new drug or treatment combination. Clinical trial protocols developed using modern study design principles have well-understood statistical hypothesis testing and internal validity characteristics. Thus, modern clinical studies are designed to deliver the most supportable scientific knowledge with the smallest number of study subjects. Despite these more efficient study designs, the complexity and associated costs of executing new protocols continue to increase.

The rising complexity of current protocols has resulted in a dramatic increase in the operational-management overhead required to initiate, execute, and complete a clinical trial successfully within budget and time frame. With the increasing number of subjects, investigators, locations, and countries involved in a given trial, it is not surprising that many clinical trials have significant operational issues that can cause substantial cost/time overruns or outright trial failures.

A distinction between scientific and operational issues in clinical trials planning and execution is important. A scientific “surprise” arises from the limited state of current knowledge about the pharmacologic and therapeutic properties of the trial agent(s) in the experimental clinical situation. This lack of scientific knowledge is precisely the reason a well-designed clinical trial is required and is ethically justified. Operational “surprises” arise because of unforeseen difficulties in executing the trial within the strict parameters or assumptions embedded implicitly or explicitly within the protocol design. In this case, the protocol designers may not have had the foresight or ability to anticipate the difficulties the field organization or clinical investigators may experience when making specific components of the study design operational.

We describe a new method for significantly reducing the risk of protocol inconsistencies and ambiguities that could lead to operational failures. This method is applied prospectively during the protocol authoring process, when changes in protocol design are the least disruptive and engender minimal cost. This method does not address:

- protocol design flaws that could prevent the study from answering the scientific question(s) posited by the author
- the ethical issues that support the need for a specific trial design
- the appropriateness of the trial in the context of a drug development plan or an important clinical problem.

The method provides a means for capturing, formalizing, and reusing an institution's implicit operational knowledge so that future proposed protocol designs can be evaluated for potential operational problems. The approach is based on encoding the features of a protocol into a highly structured, formal model of a clinical protocol that has been created specifically to capture issues that tend to cause operational difficulties. The underlying operational protocol model can be extended over time so that new institutional knowledge can be incorporated when actual field experience with new protocol designs becomes available. The model and the method described have the inherent ability to grow more capable incrementally and to protect against the loss of institutional knowledge that often follows as a result of staff turnover or promotions. After presenting the model-based protocol method, we illustrate representative findings obtained while encoding actual “near-final” protocols (protocols that have completed all internal
strained time window (such as two weeks plus or minus two days between treatment visits).

Table 1 illustrates a subset of the basic core concepts present in our current model. Although a protocol document contains many more concepts than appear in the table (such as scientific background, prior studies, statistical plan, or model informed consent form), the concepts in Table 1 were selected for inclusion in the formal model because they have direct impact on the operational features and clarity of the protocol. Over time, experience with new protocol designs and new operational issues, additional objects, and/or object attributes are added to the reviews and approvals) and the results of a validation study that supports the claim of the method’s ability to detect costly operational deficiencies prior to field deployment.

**Operational protocol models**

Current protocols are composed of a set of interrelated document sections usually created from company-specific standard templates or authoring guidelines, from cut-and-paste fragments taken from similar previous protocols, or de novo from a blank sheet of paper. A complete protocol incorporates the concerns and agendas from a multitude of stakeholders, including scientific, operational, regulatory, and marketing constituencies.

A model is a simplification of complex entities or processes that focuses on selected key attributes while ignoring or diminishing other attributes in order to highlight critical features needed to support a circumscribed set of tasks. In the case of creating an operational protocol model, we focus on modeling features, relationships, and concepts present in the protocol that have significant implications for the successful execution of the study, while minimizing or removing equally valid and important protocol features that are not pertinent to an operational perspective. For example, capturing the correct sequence of protocol-required visits, events, and milestones along with their associated tasks, data elements, and management decisions is crucial to an operational model, whereas encoding the pharmacokinetic or pharmacodynamic features of the study agent(s) is not relevant. For models that focus on drug dynamics or population effects, the opposite emphasis would apply.

We have created a detailed formal protocol model that contains a core set of operational concepts and relationships that are independent of any specific therapeutic area. In our modeling method, protocol-modeling objects represent clinical trial concepts such as eligibility criteria, visits, or tasks. Attributes that are attached to a protocol object provide definitional information about the concept represented by that object. For example, protocol events contain an attribute for detailing the specific tasks that are associated with that event. Additional attributes capture temporal relationships or constraints between two or more protocol event objects. For example, most protocols require key treatment or assessment events to happen within a highly con-

<table>
<thead>
<tr>
<th>Concept</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td>Administrative and regulatory features of a protocol.</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>A single inclusion or exclusion criterion.</td>
</tr>
<tr>
<td>Protocol event</td>
<td>Any contact with a potential or enrolled study subject. Usually a visit or any distinguished event or key milestone mentioned in the protocol.</td>
</tr>
<tr>
<td>Protocol schema</td>
<td>The sequence of protocol events with diagram temporal constraints between protocol events.</td>
</tr>
<tr>
<td>Temporal constraint</td>
<td>A temporal duration (min/max/preferred) that must hold between two protocol events.</td>
</tr>
<tr>
<td>Task</td>
<td>Any action that requires activity by study personnel or the study subject.</td>
</tr>
</tbody>
</table>

*Partial list of protocol concepts contained in an operational protocol model.*

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**Figure 1.** Protocol schema diagram displaying protocol event objects (diamonds) and temporal constraint objects (arrows). Clicking on any object in the protocol schema diagram displays the underlying details of that object.

**Figure 2.** The underlying details of the “2 day FU for Visit 1” protocol event object (diamond in upper right hand corner in Figure 1). The fields in the object specify key operational attributes of protocol events objects.
The underlying details of the protocol to be logically consistent and operationally executable. The imposed structure comprising the operational model provides a framework in which the information contained in the textual protocol documents can be placed in clear relationship to distinct protocol specifications. Any detail in the protocol that conflicts with information already encoded into the instantiated model could be a potential cause of an operational error if left unchanged. In addition, parts of the instantiated model that cannot be completed with detail from the protocol because it is missing from the protocol document also suggest a potential problem in operationalizing the protocol. That is, a protocol that is missing information required by the formal model or that contains conflicting information may generate operational deficiencies.

Our protocol modeling method classifies issues that are uncovered during the modeling process based on an assessment of how the issue could potentially affect study execution. We use a set of “impact types” for inconsistencies or missing details, which includes safety, primary efficacy, secondary efficacy, accrual, institutional review board (IRB) approval delays, administrative, regulatory, budgetary, and excessive site queries.

The model-based protocol quality improvement method proceeds as follows:

• Text protocols, created within an organization’s current protocol authoring procedures, are encoded into the operational protocol model. The modeling process involves an analyst both dissecting the text protocol and entering information according to the structure and relationships as well as the model-encoding conventions required by the elements of the operational protocol model. For example, two key components of every protocol model are eligibility criteria and visit-task associations. The operational model contains very different model structures to capture the key operational features of eligibility criteria and visit-task associations. Encoding an average protocol takes about 4–6 hours. Because our model has been tailored to focus on operational aspects of trial execution, analysts must be familiar with clinical trials concepts but not with therapeutic-specific domain knowledge.

• Because most protocol documents repeat information or offer an initial sketch with additional details provided elsewhere, the modeling of a given protocol often involves both creating new concepts and adding details to previously created concepts when more details are provided in a different section of the protocol document.

• Within each concept, the analyst may reach a feature that cannot be completed using the information available anywhere in the protocol document. In this case, critical information required to fully specify a concept from an operational perspective is deemed missing and is noted by the analyst.

• Alternatively, the analyst may reach a feature that conflicts with the substance from one or more other features or with an initial description of the feature that appears in an earlier section of the protocol document. In this case, there is a logical inconsistency within the protocol that again is noted by the analyst.

• In both cases—missing information or conflicting information—the role of the analyst is to note the issue for resolution by the original protocol author or the clinical operations team.

Assessing protocol quality using an operational protocol model

The set of concepts and their interrelationships, constraints, and other features expressed as attributes in the protocol model creates a highly structured formal representation of how the key elements of a protocol should relate to one another in order for the protocol to be logically consistent and operationally executable. The fields in this object differ significantly from the details of a protocol event object illustrated in Figure 2.

Figure 1 shows a protocol schema diagram object viewed from within the protocol-encoding tool used to enter protocol information into our formal model.10-11 The protocol schema displays a set of protocol event objects as diamonds. Arrows between protocol event objects represent temporal constraint objects. Within the authoring tool, double-clicking on any object displays the underlying structure of that object. For example, Figure 2 illustrates the underlying structure for the “2-day follow-up (FU) for Visit 1” protocol event object (the diamond in the upper right corner in Figure 1). Figure 3 illustrates the underlying details for the temporal constraint object connecting the Visit 1 protocol event object to the Visit 4 protocol event object. Notice that the structure of the two concepts (objects) is different. Protocol event objects focus on protocol-specified tasks that are associated with the event; temporal constraint objects are concerned with the allowable temporal window that can exist between two events. Model objects thus contain only those descriptive attributes that are relevant to the operational specification of the protocol.
In all instances, the analyst captures the information in an objective manner without inference or further interpretation. In addition, the model provides an opportunity for the analyst to assess the potential impact the identified issue may have on trial conduct and to suggest how the issue could be resolved or clarified in a comment object in the model as illustrated in Figure 4. It may be the case that the issue detected by the analyst was purposefully left “open to interpretation.”

The final “output” from this process is a protocol fully encoded in our operational protocol model and a report. Included in the protocol model are structured objects detailing inconsistencies and/or vague or missing information that should be reviewed by the original protocol development team. The report provides information on the exact location(s) of the issue in the protocol text and any recommended resolution of the issue. Each finding is associated with one or more impact types to highlight which aspect of the protocol the issue could affect if not addressed.

Table 2 illustrates a representative finding detected while encoding a protocol into the operational model. Each finding is associated with one or more impact types, the logical section containing the issue, a description elaborating the key issue(s), potential impact on the study if left unchanged, recommendation for clarification, and document location(s) containing the potential inconsistency or missing information.

Table 3 summarizes the distribution of findings by impact type that we have seen after applying this method on numerous near-final Phase 2 and Phase 3 protocols across widely disparate therapeutic areas. On average, encoding a protocol into the formal model elicits 28 unique findings. Most findings are associated with more than one impact type. Findings that could affect subject safety and study efficacy measures clearly are of highest concern, although each impact category in Table 3 could cause significant additional operational overhead. The number of operational issues and the distribution of impact types have remained surprisingly constant irrespective of the presence or absence of an organization’s protocol review committee.

**Method validation—a retrospective-prospective case analysis**

Table 3 illustrates the large number of operationally significant issues we have found in applying this method across a wide range of therapeutic areas and clinical trial designs. The method has produced a consistently high degree of “face validity” because clinical operations teams have reviewed the detailed findings and modified their protocols accordingly. However, prospective protocol reviews do not provide a means for sup-
porting the strong claim that the noted findings would have caused operational issues had the protocol proceeded into the field unchanged.

From a technology assessment perspective, the “gold standard” validation study will probably never be done. The strongest evaluation design would require that two versions of the protocol be randomly assigned across study sites—version 1 would be the original protocol document “as is” following all current approvals and SOPs, and version 2 would be version 1 modified based on the findings of encoding into the model. Simultaneous side-by-side execution of these two protocols would control for secular trends. Evaluation metrics would compare various trial quality and cost metrics such as the number of protocol violations, the number of operational queries by the sites to the clinical operations management team, and the number of clarification faxes, memos, or amendments required between the two types of trial sites. It seems highly unlikely that any trial sponsor would agree to perform this extremely intrusive prospective evaluation study.

Without the ability to randomize study sites to concurrent execution of two versions of the protocol, any prospective evaluation study cannot assess what would have happened had the technology been or not been used. Blinded retrospective analysis provides a compromise evaluation design that has reasonable validity, albeit less convincing than the true “gold standard” randomized prospective evaluation.

In order to address the claim that model-based protocol encoding can detect operational issues that affect trial execution in a reasonable, rigorous manner, we performed the following retrospective-prospective analysis:

- An independent third party selected two completed protocols that had incurred a number of amendments during their execution. Protocol #1 had four amendments; Protocol #2 had six amendments at the time of selection. The modeling team was not involved in the selection of the two retrospective protocols. Note that the two chosen protocols were from different therapeutic areas, designed by different protocol authors, and managed by different clinical operations teams.
- The modeling team was given only the first approved version of the protocol document that was sent to the clinical trials sites at the start of each trial. The modeling team had no access to any of the amendments that occurred subsequent to this initial protocol version.
- The model-based quality assessment method described previously was applied to the two protocols, generating 35 findings for Protocol #1 and 34 findings for Protocol #2.
- The findings were sent to the independent third party who compared them with the complete set of 10 amendments that occurred during the execution of the two trials. Because each amendment addressed several distinct issues, the reviewer determined which issues could be deemed “operational” versus “scientific” versus “regulatory” and then compared the findings from the blinded encoding process to the actual operational issues. The modeling team had no involvement in the classification of amendment issues or in the evaluation of the amendment issues to the encoding findings.

Figure 5 provides the combined results from both retrospective comparisons. A combined total of 69 findings were generated from encoding the two initial protocols into the operational protocol model. The independent reviewer deemed 15 of these findings to have matched operational issues addressed within the 10 protocol amendments. A number of issues present in the 10 amendments dealt with either expansion to the study population or protocol design changes caused by regulatory review and were not within the scope of our operational model. Two issues deemed by the independent reviewer to be operational were present in the amendments but were not detected by encoding the protocols into the operational model (Figure 5, lower left corner).

In addition to the 15 issues in the retrospective models that matched those in the subsequent amendments, the reviewer noted that many of the remaining 54 issues identified in the final report were also relevant issues for the clinical operations team even though no formal amendments were generated. Quoting from the independent reviewer’s comments: “Both pilots serve to demonstrate that the [operational model] can identify many protocol elements that could be made clearer and thereby avoid confusion or execution errors, or make the protocol easier to use. Not all of the findings will be of the magnitude that their implementation would avoid amendments, but many would help avoid protocol violations and promote smoother execution.” Smoother execution would translate operationally into fewer telephone calls, memos, and faxes between clinical operations team members and the clinical trials site to clarify confusing operational issues. Issues that can cause the clinical operations team additional overhead and management time but not generate formal protocol amendments are also detected using the model-based encoding method.

**Protocol review committees**

At most large clinical development organizations, concern about protocol design quality has spawned the creation of protocol review committees (PRCs). Although specifics vary widely, the role of the PRC is to provide a centralized resource for the criti-

![Figure 5](image-url)
As people leave the organization, the institutional knowledge drawbacks that significantly limit their usefulness:

Organizational mergers and alliances result in widely disperse approaches, assumptions, and standard operating procedures for designing protocols. Operational knowledge unique to one organization or to a specific therapeutic area tends to remain within the original organization or therapeutic area and therefore not benefit the combined organization. The diffusion of hard earned (and expensive) experience-based knowledge occurs only if and when people from one organization migrate into similar positions within the second organization. Of course, this migration results in the loss of operational knowledge from the original clinical operations group. Only by compiling organizational knowledge into a “learning” system can the current zero-sum situation be converted into an additive experience environment.

Operational deficiencies can be costly to an organization in many ways. Although no formal literature has been published estimating the direct and indirect costs of protocol amendments, anecdotal evidence suggests that even simple amendments have substantial costs, with estimates ranging from $80,000 to $200,000 total. Included in these estimates are the resources required to create, distribute, and communicate changes in any study artifact (revised protocol, list of changes, modified informed consent form, changed case report forms, updated study manual, or other site materials), additional site negotiations and logistics (site contract and budget renegotiations, updated site procedures, additional study materials, study subject reconsents, and full or expedited IRB reviews), and site performance (loss of potential or current study subjects; loss of site interest and momentum). Although many of these time and cost factors are difficult to measure directly, any one of these issues can cause an amended protocol to affect planned budgets, promised milestones, and desired clinical results.

Amendments are only the most visible and most costly manifestation of a spectrum of ways in which operational deficiencies can affect an organization. A large number of operational issues are handled via formal and informal communications between study project managers and clinical trials sites. Thus, the volume of faxes and telephone calls can be another “cost” that directly affects team productivity and trial site performance but is not as visible as a trial amendment. Two additional indirect effects of operational deficiencies could include a decrease in the quality or acceptability of clinical trial data, and additional regulatory comments regarding protocol clarity or deficiencies.

No published literature has examined the impact of PRC reviews on the quality of protocols following their review. We have anecdotal evidence of a small reduction of the number of operational issues identified by the model-encoding method on protocols created after the introduction of a PRC compared to similar protocols created prior to the institution of a PRC at a single sponsor organization. PRC reviews do seem to make a positive contribution to the operational quality of reviewed protocols, but at an unknown cost.

PRCs generally require highly trained, expensive senior people to perform time-consuming, detailed review of every protocol prior to internal approval. The staff time consumed in reviewing a proposed protocol, discussing the findings at a PRC meeting, presenting the findings to the protocol author, and then repeating the process in a limited manner after the protocol is revised represent a huge hidden cost. As PRC members leave or rotate, the quality and quantity of protocols reviewed by the PRC may vary widely. While PRC reviews may be effective, they are neither scalable nor repeatable.

The formal model used to encode a protocol can be expanded by using new protocol-modeling objects when new operational concepts appear in new protocol designs. Nothing in the current operational model is specific to therapeutic areas, although various protocol concepts and designs may be used more commonly

Protocol review committees represent an enormous investment of highly trained personnel.

representatives from clinical operations management teams and some include representatives from clinical trial sites.

Although no scientific study exists that documents the impact of PRC reviews, there is persuasive anecdotal evidence of their value. Many organizations that have implemented PRCs now require every protocol to be reviewed and approved by the committee prior to its release to the clinical operations team for field deployment. In addition, many PRC members state that a review by the committee often results in substantial changes to the original protocol. Protocol review committees bring together substantial skills and institutional experience, representing an enormous investment of highly trained personnel. For the organizations that have committed to this approach, the investment is deemed justifiable, given the high stakes and resources committed to the execution and success of each trial.

In addition to or instead of forming PRCs, many organizations have instituted other methods for improving the quality of a protocol during its initial creation. Templates, checklists, and previously approved protocols are common materials provided to protocol authors to assist with the improvement of the quality of their initial protocol designs. These methods have numerous drawbacks that significantly limit their usefulness:

- Most paper-based methods are static. That is, these methods are not easily updated, disseminated, and incorporated into the protocol writer’s daily routine. Protocols developed with these tools often continue to repeat the same operational mistakes long after the organization has updated the reference materials.
- As people leave the organization, the institutional knowledge of what makes a protocol “work” within that organization is lost. If the employee was a member of the PRC, this loss of institutional knowledge is even more extensive, affecting the entire range of protocols reviewed by the PRC.
- Organizational mergers and alliances result in widely disparate approaches, assumptions, and standard operating procedures for designing protocols. Operational knowledge unique to one organization or to a specific therapeutic area tends to remain within the original organization or therapeutic area and therefore not benefit the combined organization. The diffusion of hard earned (and expensive) experience-based knowledge occurs only if and when people from one organization migrate into similar positions within the second organization.
in specific therapeutic areas. In addition to using new protocol objects, new attributes can be added to existing ones or relationships between them defined. These new attributes and relationships then become part of the description of the protocol that must be filled in by the analyst while encoding subsequent protocols. In addition, the method that guides the analyst to discover operational concerns grows incrementally with the addition of new conventions and rules that codify learned knowledge. For example, in Figure 5 (lower left corner), we noted that two operational issues present in the retrospective amendments were not detected during protocol encoding. These two missed operational issues were analyzed and new protocol elements were added to the model. “Learning” that will be applied to all future protocol encodings was thus incorporated into the model.

Subsequent protocols use the operational model to ensure their internal consistency. What is reused across future protocols is the expanded operational model, not trial-specific content from previous studies. Despite differences in trial objectives, phase, or study design, later protocols can benefit from being encoded into the operational model.

By extending both the protocol model and the methodology, formalized institutional knowledge about trial successes and failures applied to later trials increases in breadth and depth. Over time, the model and methodology will grow to represent more operational “experience” across a wider range of company-trials activity than the operational knowledge that currently exists within any single therapeutic area, closing the gap between therapeutic-area-specific silos of institutional knowledge.

We have presented a method for analyzing a protocol for operational completeness and clarity. By encoding a protocol’s content into a formal representation of the key operational concepts and features—both as model objects and as attributes of a knowledge base of logical consistency rules—we detect inconsistencies and missing information that could have significant operational impact. Encoding a wide range of protocols from a variety of therapeutic areas has shown that this method is useful without requiring specific knowledge of a therapeutic area. In a retrospective analysis blinded to subsequent amendments and trial contact logs, numerous findings detected by this method were shown to predict a significant number of the operational issues that caused difficulties for the project team during actual trial conduct. The formal model provides an explicit structure in which a protocol can be dissected and analyzed. The model and method provide a means of incorporating new knowledge of novel protocol designs and also capture institutional knowledge that currently resides in the corporate culture.

The next step in this method is to replace encoding of protocols that were created using standard word-processing environments with model-based protocol authoring. By moving to direct model-based protocol authoring, the number of ambiguities and inconsistencies we currently detect from traditionally authored protocol documents would be expected to decrease dramatically. Because a model-based authoring approach enforces a formal clarity and an “encode once; reuse many times” discipline, many of these inconsistencies would simply not arise or would be detected as soon as they were introduced during protocol authoring. In this new authoring environment, the number of operational issues should decrease significantly, producing operationally cleaner and more clearly understood protocol documents.

References

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