Promoting Patterns

Poor management of data is one of the factors ailing adverse event and endpoint adjudication in clinical trials. How can developing and validating control and event patterns help clear the confusion?

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The clinical trial industry is transforming, and the vision for this is simple: embrace quality and automation across the clinical trial spectrum and move closer to zero-delay trials. Why? It provides better, faster results, offers more information for sponsors, allows more innovation for CROs, and, most importantly, presents expedited outcomes for patients in need. This transformation is just beginning and requires that we challenge ourselves, our teams, partners, and clients – the entire clinical trial industry – to work smarter and eliminate preventable delays.

Clinical trials are complex, multi-year logistics exercises resembling roaring rapids more than Olympic synchronised swimming events in a placid pool. An average Phase 3 oncology trial may include a sponsor team talking to a CRO team talking to dozens or even hundreds of investigator sites spread across a few dozen countries that, in turn, must recruit patients and ensure that they follow the strict protocol guidelines necessary to carry out the experiment in question. Add to this a good dose of language and cultural differences and one wonders how a drug, biologic, or device is ever approved by regulatory agencies; in fact, most are not. Reasons for clinical trials failing to produce expected or desired outcomes may often lie in the scientific hypothesis. Nonetheless, it must sometimes be considered whether the process of data collection and evaluation plays a role in failure.

Data Dilemmas

Drug or device trials are fundamentally science experiments. Everyone has some familiarity with how that works from those exciting high school or college labs where one measured some Newtonian physics principle. However, unlike those, in clinical trials, the outcome is unknown, and the data are never as crisp and predictable. For the most part, the signal-to-noise ratio is exceedingly small. If the data collection or the analysis processes adds more noise to the system, the signal may become undetectable. When that happens, therapies that might have helped patients in need may never be approved because the data was not handled appropriately.

The industry has tackled this problem through automation. For years, numerous IT companies have developed important tools to help sponsors and CROs manage the data they collect, ensuring that every system interaction is properly logged so analysis can be performed to find and correct shortcomings in the data gathering process. Unfortunately, digital data gathering remains a complex problem, and just being able to 'replay' the actions taken by trial managers, coordinators, and investigators does not simplify the problem enough – take adverse event or endpoint adjudication processes for instance.

Errors in Judgement

Determining whether an event is the result of the drug being tested is an elaborate process. It involves collecting documents from investigator sites, determining whether they are complete, and putting together subject dossiers. The latter are then used to enable adjudication workflows. In some cases, adjudicating an event is implemented as a kind of 'voting' process involving individual 'adjudicators' and clinical event committees (CEC) to break ties. At times, the dossier is distributed to an odd number of adjudicators voting independently, where majority wins. Other methods may allow an even number of adjudicators to communicate with each other under certain constrained situations, enabling one or more of them to change their vote to achieve concordance. The types of workflows available to adjudicate events are almost infinitely variable and reflect the preference of individual adjudicators or the chairs of particular CECs.

The complexity of these adjudication workflows makes it difficult to validate the technical implementations that manage these processes. Moreover, different groups within sponsor companies and CROs adjudicate the same type of event differently. The varying adjudication of events of the same type across different clinical trials that are managed by the same operations group further exacerbates the situation. In short, there are no standard practices. A death event in oncology protocol – one managed by CRO X for sponsor Y – is likely adjudicated differently by the same CRO for the same sponsor for oncology protocol two in the same drug programme. Using different adjudication methods in cases like this prevents everyone – from sponsors all the way to regulators – from developing any kind of predictability or repeatability, creating instead obfuscation that makes it harder to determine outcomes. This, in turn, greatly increases risk in clinical trials. Stories abound of clinical trials whose compound seems to have failed only to be rescued by re-adjudication processes that could better understand endpoints.

Troubleshooting

The answer to this problem is not obvious. The tension between flexibility and predictability is high, with sponsors and CROs arguing that every trial is different and regulatory agencies needing an objective way to analyse results and reach valid conclusions in increasingly complex studies.

After observing the many different adjudication workflows used across a variety of sponsor and CRO trials, the fact that divergence in workflows is influenced by issues of control

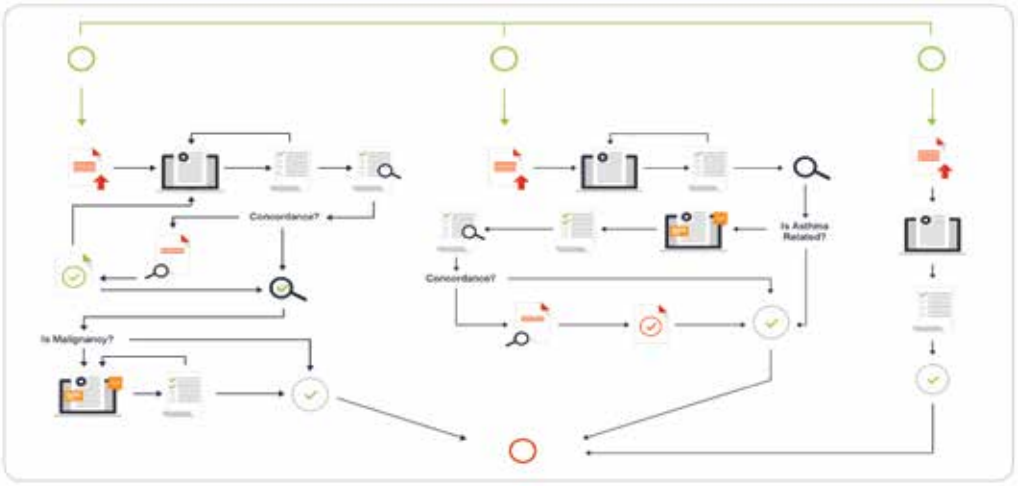

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Figure 1: The complexities of endpoint adjudication

and trust is evident. For example, a relatively simple two-adjudicator workflow followed by a CEC evaluation in cases of discordance can be made more complex when the CRO requires the completed voting eCRFs to be reviewed in-house before they are made available to the clinical event committee. Whether this extra set of steps is necessary or not is not in question. What is true is that the addition of this set of steps generates data (eg when were the forms sent, who reviewed them, what was the outcome of the review, when was the dossier made available to the committee), and this data gets clumped together with the data generated by the disposition of the case under its normal workflow. This additional workflow snippet does not modify the two-adjudicator and CEC pattern; it is just a control overlay on top of it. Nonetheless, if it is not recognised as such, it only serves to obfuscate the information that is central to the premise of the trial in question.

The answer to the validation and flexibility conundrum lies in reusability and patterns. Reusable patterns have been used in the field of software engineering for many years and have injected a level of reliability and predictability when testing complex system implementations. Software design patterns can be augmented by decorator patterns, which are applied to enhance or add functionality to basic design patterns without necessarily changing their core behaviours.

Developing Patterns

One suggestion is that event patterns be defined to handle specific event types. These may include the two-adjudicator and the CEC pattern and many others, such as an odd number of adjudicators with majority rule. Additionally, control patterns should be defined as overlays on top of event patterns to add various kinds audit/control related actions. System and user action logs, which record every interaction with and by the adjudication system, can then be reported either in the aggregate (as it is done today) or by segregating actions depending on whether they were part of event management or control workflows. By enabling event and control patterns, sponsors and CROs are able to retain the level of flexibility they need to carry out their studies. Concurrently, being able to separate system interactions by pattern type enables sponsors and regulators to look at significantly clearer data, thus structure where before they saw noise.

Creating event and control patterns cannot be done reliably using traditional computer languages. The complexity is too high when expressing these concepts in Java, C++ or similar development environments. An electronic endpoint/event adjudication system (EAS) must be able to represent these patterns using higher level semantics (eg graphically) with facilities to place the control overlays and enable the decoupling of audit logs when necessary. For the industry to be able to adopt this adjudication management functionality, the patterns must be defined and validated, and it should be clear that they are being used and implemented in the EAS without modification. This will, in turn, reduce the time it takes to launch complex adjudication projects and the level of errors as well as minimise the time it takes sponsors and regulators to determine the direction of particular experimental therapies.

Industries pursuing transformation need vision and aspiration. Data quality in clinical trials is paramount. Whether collecting patient scans as surrogate endpoints or collecting patient data for serious event or endpoint adjudication, guaranteeing this data is devoid of errors can mean the difference between success and failure. We must remain focused on continued innovation and entrepreneurship in our industry. Delays and mistakes must be scrubbed out of the process. If those principles can be agreed upon, moving closer to zero-delay clinical trials is possible.

About the author

Abraham Gutman founded AG Mednet in 2005 and leads the company's mission to improve, automate, and expedite outcomes in clinical trials by ensuring quality and compliance within drug, biologic, and device trials. Abraham holds a BA in computer science from Cornell University and an MSc in computer science from Yale University, US.

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