Performing High-Risk Mid-Study Changes that Impact Randomization and Trial Supply Management

Sponsors continue to face significant challenges with the volume, complexity and risk of mid-study changes to their randomization and trial supply (RTSM) designs. If performed incorrectly, these pose serious consequences, such as protocol deviations and patient safety issues. Prolonged amendments cause costly study delays and inconvenience sponsors, sites and patients; starting up new cohorts or arranging patient visits may be postponed. Therefore, it is of critical importance that system changes are rolled out efficiently, on time, and with complete accuracy.

There are extremities in the ways RTSM vendors handle mid-study changes, and Veeva strongly opposes these approaches. Some take an oversimplified route and provide misleading messaging on just how quickly a change can truly be made. Others lack the product capabilities and services resources to achieve these in an acceptable time frame, taking weeks and even months to implement.

These challenges are not going away. The Tufts Center for Study of Drug Development (CSDD) recently reported that the number of mid-study amendments, including substantial amendments, continues to increase across all trial phases. Therefore, RTSM vendors must be equipped to sufficiently handle all types and complexities of changes.

This article is predominantly focused on high-risk changes that impact patient treatment assignments. These may be expected, for example in adaptive or dose finding trials where expected changes are already baked into the protocol design. Or they may not have been pre-defined and are the result of a protocol amendment.

- Adding Dose Levels
- Adding Cohorts
- Adding Treatment Arms
- Adding Kit Types
- Adding Visits / Extension Period

Veeva RTSM strongly advocates that the need for speed should be balanced with a need for rigor. There are repercussions if these changes are handled too hastily or too laboriously.

Performing high-risk changes ‘in minutes’

When vendors claim that a new dose, arm, cohort, kit or visit can be added to a live study via a self-service feature in ‘just minutes,’ this is simply too good to be true. There are many areas being overlooked if this is genuinely being added on the fly. Alternatively, the vendor is marketing the time taken for the technical changes only without reflecting the true end-to-end timelines.

Systems may have a product feature that appears straightforward in the user interface, such as a button for the sponsor to simply 'add' the dose, arm, cohort or visit on demand. If a dose needs to be added, there is far more to consider than simply adding a dose record with the correct dose name. For example:

- What visit(s) and treatment arm(s) is this dose associated with?
- Are there any titration rules to consider?
- What kit types are being used for this dose?
- Are resupply plans inclusive of this dose?
- Is there any impact on existing patients to consider?
- Is this dose active across the whole study or are only certain IRB approvals in place?
- Does a new cohort need to be added, too, for this dose design?

This approach also fails to appropriately document the change and fully validate that it performs as expected, including any regression testing. The functionality may be considered prevalidated, but the configuration must still be documented and reviewed; the stakes on getting this incorrect are too high to disregard. Protocol deviations may occur, and patients may be mis-dosed or mis-treated.

Many systems boast a self-documenting feature for these types of amendments. Having the system directly document the change is also extremely risky. What if the configuration is performed incorrectly? This means the resulting documentation is also incorrect and errors may go undetected.

These types of changes have a direct impact on patient treatment and failing to wrap a robust documentation and validation process around them is dangerous and irresponsible. Product features claiming to achieve changes in minutes demonstrate very well, but in reality they have no value and meaning without surrounding processes.

Challenges with timelines

In contrast to the 'changes in minutes' approach, other vendors may require several weeks to even begin resourcing a change, meaning implementations take several months. The time to administer a change may take as long or longer than the initial study design. Inadequate resource models, inefficient processes and a lack of system configurability are usually culpable for such lengthy delays.

When vendors are focused on achieving new study awards and start-up timelines, it is challenging to provide quality resources to work on mid-study amendments quickly. If resources are reallocated to work on changes, this puts new study FPIs at risk. Inflexible service structures will lead to one or the other being neglected, and often it is the study that has already been awarded that is de-prioritised. Not only are amendment timelines then put at risk, but relationships will also become frayed.

A lack of system configurability can also result in these lengthier timelines. Although documentation and validation are usually rightly in place, if system changes take even further time due to custom coding and securing programming resources this exacerbates the timelines. Ultimately this more labor intensive method puts the amendment at risk, can delay the study and frustrates sites and patients in the process.

Veeva RTSM's approach

Veeva RTSM has defined best-practices to responsibly and efficiently manage high risk design changes. Mid-study changes require a product flexible enough to implement them with ease and expert services to document and deliver accurately within expected timelines. Offering an RTSM system that is able to implement these changes in minutes, while technically feasible, simply does not align with Veeva's values of Do The Right Thing and Customer Success. So we offer a balance between speed and rigor.

Speed:

Immediate Resource Allocation: Veeva RTSM is delivered by a dedicated services team. They are structured with flexibility to ensure a named resource is immediately available to assess and work on any change requests without compromising new study start ups.

High Configurability: Veeva RTSM is highly configurable. The technical aspect of the change can often be configured within minutes to hours. But we appreciate there are further processes required for the end-to-end process and therefore do not market that we can make high risk changes at this speed.

Known but Undefined (KBUs): Studies that anticipate additional cohorts or dose finding designs can benefit from KBUs in the initial study configuration. Fields are proactively set up during the build where the need is known but the entry or value is still undefined (for example, there will be a new dose but that dose is still undefined). KBUs help accelerate the configuration, documentation and validation processes.

Streamlined Validation: Veeva is investing in automated validation methods that will complement our traditional validation processes and allow for fast, reliable re-validation of an entire project as needed.

Rigor:

Impact Analysis: Knowledgeable design teams will evaluate the full impact of the change request to ensure there is no adverse effect on other design elements (for example, on roles, permissions, blinding, reporting, etc.).

User Requirements Documentation: Changes are thoroughly documented in the User Requirements Specification (URS) with clear version control. This has been streamlined to be an easy to understand yet fully detailed document <100 pages. Using Veeva Vault, all RTSM project documentation is easy to distribute, access, review and sign electronically.

Complete Validation Package: Full validation documentation will be provided for the changes made, ensuring regulatory compliance and assurance that critical changes have been accurately implemented as documented in the URS.

Additional considerations

There are many changes that Veeva believes should be self-service throughout the study lifecycle. Veeva RTSM provides an intuitive end user interface to perform these on demand. This includes changes such as:

- Additions or changes to resupply plans
- Opening/closing cohorts
- Amending caps
- Inventory management (releases, expiry updates, relabeling, kit status changes)
- Patient data changes (based on the protocol)
- Adding sites, countries, depots and users

This is not an exhaustive list, but these are common examples of lower-risk changes that can be performed by permitted users in our validated solution with a full audit trail. Safety nets can be put in place to mitigate risks (for example, alerts on data changes).

There is also less risk when it comes to adaptive changes such as dropping arms or doses. Switching elements off is simpler than adding new ones. Often this can be managed through updates in the end user interface or through much faster helpdesk-driven configuration changes.

Conclusion

Veeva RTSM firmly believes that higher-risk amendments require flexible product capabilities, well defined processes and expert services resources to deliver these successfully. This should never be completed only through a self-serve product feature that claims it can be done in minutes. Nor is it acceptable for changes to take several weeks of laborious costly efforts. Veeva's approach provides a robust and timely implementation, ensures regulatory compliance, and most importantly protects patient safety and study integrity at all times.