Veeva

WHITE PAPER

Complex Change Requests

Repeatedly moving with speed, quality, and precision

A small biotechnology company is currently running a Phase 1 dose-escalation and expansion study, starting on paper from the initial protocol to the addition of 4 amendments, before expanding scope enough for an RTSM system to be required for any further study activities. They have a history of needing to pivot their study design and will need a system that can continue to change with speed, quality, and precision to match the evolving requirements of their protocol.

01. Implementing RTSM Functionality on an existing study

Existing Study Data Lives on Paper

CHALLENGE	SOLUTION
The small scope of the initial protocol and subsequent amendments could easily be managed on paper and did not require an electronic system. As new data emerged during study execution, the sponsor continued to add new endpoints into the existing protocol and expand the patient count. With up to 120 potential patients in the latest amendment, the value of an RTSM system could be justified; however, the system can collect net new data but historical data is currently on paper. The RTSM system will also need to upload historic information to ensure data is harmonized and given a central repository, where the old data can be leveraged for reporting and other needs.	Veeva RTSM was able to upload historical data into the system at initial Go-Live to ensure any patient, event, kit, batch and shipment data was available for reporting. Veeva Subject Matter Experts considered historical and new design elements to ensure both old and new patients could progress as needed.

Complex Initial Study Build

CHALLENGE

After award, the study was initially built, designed, and approved based on Amendment 5 of the Protocol. The study design contained the following key design elements:

- **Indication/Cohort 1:** Dose escalation in 2 arms (Arm A, Arm B; each containing 18 subjects), selectively enrolling subjects who are not (Arm A) or are (Arm B) receiving alternate therapy. Additional subjects will be enrolled into two expansion cohorts using Recommended Phase 2 Dose (each containing approximately 12 subjects).
- **Indication/Cohort 2-4:** Dose escalation per cohort in a single arm. Additional subjects will be enrolled into two expansion cohorts using Recommended Phase 2 Dose (containing approximately 20 subjects per cohort).
- **Treatment:** Receive treatment daily in 28-day cycles until disease progression.
- **Dose Levels:** 13 dose levels of varying strengths (x mg) and frequency (e.g. QD, BID).
- **Investigational Product:** Study IP is supplied as 25 and 100 mg strength capsules for oral administration stored in 30 capsules per bottle for both 25 mg and 100 mg capsules. Bottles are provided in a kit which may consist of the combination of the 25 mg and/or 100 mg capsule bottle.
- **Kit Types:** 13 kit types; one for each of the 13 dose levels.

During the design phase of the RTSM, the sponsor had concurrent discussions about their current IP packaging as bottles supplied in a kit configuration helped the sites and patients ease of dispensation, but it was proving too costly in drug wastage. Certain levels were not being used as frequently as others, causing them to be unused before expiry. Alternatively, individual bottles within the kit packaging would expire and render the rest of the bottles in the kit unusable as well. Although not approved yet, the sponsor knew a protocol amendment 6 would be coming shortly to resolve this issue which would introduce 2 new kit types for the 25mg and 100mg bottles to be packaged and labeled individually. Only these two kit types will be used for Amendment 6 and the bottles in a kit configuration will be sunset.

SOLUTION

Veeva RTSM was built including cohort management functionality which allows end user self-service control over study design elements being explored. End users can open cohorts for enrollment to choose what can actively be explored or close cohorts to create a pause for data review and analysis. Alternative dose levels were built in to allow pivoting of dose strength and frequency as the study progresses and new, more accurate data is made available. Capping is leveraged to create a 3+3 escalation design or manage any time sensitive requirements between patients and a dynamic selection of the recommended phase 2 dose is available to end users when determined.

Building on our experience with this study and others, Veeva RTSM now empowers end users with self-service control to dynamically create cohorts and dose levels in real time. This innovation gives study teams even greater agility and control, allowing them to seamlessly adjust study design elements as new data emerges. See it in action.

Timing of New Functionality

CHALLENGE	SOLUTION
The new kit types and system functionality should only be made available to sites individually as they approve the latest Amendment 6. If given too early, sites who have not approved the amendment will get access to kit types and functionality they should be restricted from. If given too late, sites who approve the amendment will not get access to the latest kit types and functionality and delay their access until the last site is approved.	Addition of a custom site field for Site Protocol Version to designate if they are on 'Previous Protocol Amendments' or 'Amendment 6'. Sites on 'Previous Protocol Amendments' will be resupplied and dispensed the old bottles in a kit configuration while sites on 'Amendment 6' will be resupplied and dispensed new individual bottle configuration. This allows the sponsor to only grant new functionality per site and follow the approval process individually. This field was also used strategically at times to ensure the previous bottles in a kit configuration were used to their fullest to minimize drug wastage.

02. Adding New Kit Type, Dose Level and Priority Dispensing

New Kit Type

CHALLENGE	SOLUTION
A new protocol Addendum 6.1 added a new kit type, 200mg capsules in a bottle, which was needed for more efficient dispensation of IP based on the higher dose levels currently being actively explored.	A new kit type was added for 200mg capsules in a bottle. The Veeva Services Team works with the sponsor to ensure a smooth rollout including coordinating adding resupply values for existing sites or making it an operational step after deployment of the changes.

New Dose Level

CHALLENGE	SOLUTION
A new dose level is needed for exploration of new data. A typical request found in dose escalation studies.	A new dose level was added for dynamic selection in existing cohorts if needed to be explored.

Kit Type Combinations

CHALLENGE	SOLUTION
With bottles now being individually dispensed, there is a need to determine the most efficient kit type combinations to dispense per dose level as there are many possible combinations. Rather than choose a single combination per dose level, the sponsor wants to prioritize certain combinations but use secondary (or further) combinations if the initial is not available to prevent stock out.	A priority dispensing was developed for each dose level to allow multiple combinations to be attempted for dispensation in a specific order, stopping after its first successful match. The sponsor hoped to prioritize the larger strength capsules when possible, such as 200mg over 2x 100mg but if 200mg is not available, 2x 100mg can be dispensed to prevent stock out. Veeva Subject Matter Experts used this information to provide multiple kit type combinations to the Sponsor to prioritize. Some combinations were not used if excessive quantities were needed (e.g. 8x 25mg will not be used to substitute for 200mg). Some dose levels ended with up to 7 possible kit type combinations before stock out would be allowed.

Timing of New Functionality

CHALLENGE	SOLUTION
New kit types and system functionality should only be made available to sites individually as they approve the latest amendment.	A new value was added to the Site Protocol Version field for Addendum 6.1. Sites on 'Addendum 6.1' will be resupplied and dispensed the new 200mg bottle configuration as well as use the priority dispensation functionality. New functionality will continue to be granted per site and follow the individual approval process.

Speed of Changes

CHALLENGE	SOLUTION
Every day a trial is delayed, the sponsor can lose up to 1 million dollars so speed, while maintaining quality, is always an important factor in execution. The sponsor requires the changes to be made in a timely manner and ensure the RTSM is not the rate limiting factor to operations beginning again. All system changes must be executed at the pace operations dictates.	To normalize what we are comparing, the dates used will be from customer approval to begin design to UAT completion. The addition of a new kit type, a new dose level, a priority dispensing of kit types for all 13 dose levels (with up to 7 different combinations for some) and integration of the changes in a site protocol amendment field to ensure a site level rollout of changes was completed in 20 business days.

03. Introduction of Bioequivalence

Introduction of Bioequivalence

CHALLENGE	SOLUTION
A new protocol Amendment 7 was added for the introduction of a bioequivalence end point. New tablet kit types will be added to match capsule kit types of 25mg, 100mg and 200mg. The sponsor will need to support each kit type across all sites and allow a selection per patient at screening to choose their kit type formulation for the duration of treatment.	New tablet kit types to be added to match capsules kit types of 25mg, 100mg and 200mg in a bottle.

Timing of New Functionality

CHALLENGE	SOLUTION
New kit types and system functionality should only be made available to sites individually as they approve the latest amendment.	A new value added to the Site Protocol Version field for Amendment 7. Sites on 'Amendment 7' will be resupplied and have the option to be dispensed new 25mg, 100mg and 200mg tablets in a bottle configuration per patient. New functionality will continue to be granted per site and follow the individual approval process.

Kit Type Combinations

CHALLENGE	SOLUTION
Rather than choose a single combination of kit types per dose level to dispense, the sponsor wants to prioritize certain combinations but use secondary (or further) combinations if the initial is not available to prevent stock out.	The same priority dispensing developed for capsules was applied to tablets as well. As only the formulation was changing, the same kit strength combinations could be used as before.

Speed of Changes	
CHALLENGE	**SOLUTION**
A continued need to have all RTSM system changes executed at the pace operations dictates while maintaining quality as the highest priority.	To normalize what we are comparing, the dates used will be from customer approval to begin design to UAT completion. The addition of 3 new kit types for tablets, a matching priority dispensing of kit types for all 13 dose levels for tablets as capsules and integration of the changes in a site protocol amendment field to ensure a site level rollout of changes was completed in 20 business days.

Conclusion

Oftentimes sponsors may have known areas of their protocol which contain unknowns which can be creatively designed to change easily via dynamic, end-user controls of these elements in the system. Protocols also often turn in directions that can not be foreseen, so having a RTSM that can pivot and execute change requests with speed, quality, and precision to match the evolving requirements of the protocol is essential.

These are the essential pillars which must be executed with complex RTSM change requests:

Speed

To ensure operations are not waiting for system updates before they can begin, as illustrated in the ability of Veeva's RTSM to work with roll outs of amendments.

Quality

To ensure patient safety, the blind and/or supply management is not affected.

Precision

To ensure the mark is repeatedly hit as multiple change requests may be needed during the life of a trial.

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