Dose Escalation/Early Phase Studies

A main goal of Phase 1 trials is to establish the recommended dose and/or dosing regimen of new drugs for efficacy testing in phase 2 trials, using a detailed and monitored dose escalation process. To reach this endpoint, study designs will have many components of this process outlined in the protocol, including starting dose/regimen, dose levels, dosing regimen, titrations, dose escalation method, number of patients per dose level, the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D).

As Phase 1 trials represent the first application of a new drug to humans, the protocol will be a list of potential options to be explored for each component based on the limited information available. However, the Sponsor will need to control how and when these components will be used as the study progresses and new, more accurate data is available. Breaks in enrollment will often be needed during these evaluation periods while key personnel, such as a Dose Escalation Committee, reviews the latest data and determines what components may be explored next by new subjects.

In these scenarios, Sponsors require adjustable and self-service controls to these components in their RTSM to ensure their systems can change and move at the pace their operations dictate. They cannot wait and be reliant on 3rd Party support for such changes or else RTSM could become a rate limiting factor.

Solutions

For each of the components below, we can see how Veeva RTSM can help solve these problems with an example solution:

Starting dose/regimen – Ability to open and close cohorts allows Sponsor to control which dose level and/or dosing regimen is actively being explored. Sites will only have access to enroll subjects when at least one cohort is open. When only one cohort is open, Sponsors can force sites/patients into the one available cohort (e.g. during dose escalation). When multiple cohorts are open, Sponsors can allow the sites/patients to select the cohort to enroll (e.g. during dose escalation based on patient disease type). Different workflows can also be configured to allow Sponsors to select the cohort to enroll, to quality gate the process.

Cohort Information

Cohort ID:	2
Cohort Name:	Cohort 20mg
Export Name:	COHORT 20mg
Dose Level:	20mg ⌄
Max Total Subjects:	3
Is Active:	✓ False / True

Dose levels – Protocols may often list primary dose levels which may be explored but will also state the Sponsor can explore any dose levels between these ranges should it be needed. Cohorts for Primary and Secondary dose levels can be built into the RTSM for quick pivoting of active dose for exploration. If good results were seen in one primary dose level, but many Dose Limiting Toxicities occurred in the next, escalated dose level, a secondary dose level may need to be explored between these two primary levels to find the most accurate MTD/RP2D. It's important to have the flexibility to quickly pivot to explore additional dose levels without waiting for an update to the RTSM.

Cohorts

Export   Rows: 13

	Cohort ID	Cohort Name	Export Name	Dose Level	Max Total Subjects	Total Subjects	Is Active	
🔗	1	Cohort 10mg	COHORT 10mg	10mg	12	12	False	↺
🔗	2	Cohort 20mg	COHORT 20mg	20mg	5	5	False	↺
🔗	3	Cohort 30mg	COHORT 30mg	30mg	3	0	False	↺
🔗	4	Cohort 40mg	COHORT 40mg	40mg	3	0	False	↺
🔗	5	Cohort 50mg	COHORT 50mg	50mg	3	0	False	↺
🔗	6	Cohort 15mg	COHORT 15mg	15mg	3	0	False	↺
🔗	7	Cohort 25mg	COHORT 25mg	25mg	3	0	False	↺
🔗	8	Cohort 35mg	COHORT 35mg	35mg	3	0	False	↺
🔗	9	Cohort 45mg	COHORT 45mg	45mg	3	0	False	↺
🔗	10	Stage I	STAGE I	20mg	24	3	True	↺
🔗	11	Stage II	STAGE II	20mg	24	1	True	↺
🔗	12	Stage III	STAGE III	20mg	24	0	True	↺
🔗	13	Stage IV	STAGE IV	20mg	24	0	True	↺

Dosing Regimen – Similar to dose levels, protocols may list multiple, primary dosing regimens (e.g. Q2W, Q4W) but give discretion to the Sponsor to explore secondary dosing regimens if needed (e.g. Q3W). Cohorts for Primary and Secondary dosing regimens can be built in for quick pivoting of dosing regimens for exploration.

Titrations – Sites or Sponsors can manage patient specific titrations after their initial starting dose. This ensures patients can titrate to the safest and most therapeutic dose level based on their individual response. The system will be setup to only present applicable titration levels for change based on the study rules (e.g. stepwise titrations).

Record Subject Event

Site Number:	101
Subject ID:	101-004
Date of Birth:	11 Dec 1958
Sex:	Male

Please confirm the following data, then select the event you wish to record:

Confirm Subject ID:	101-004

Event Date:	27	Feb ∨	2024
Event to Record:	Week 4 ∨		

Current Dose Level:	10mg

Dose Level Option:	Increase the current dose level ∨
New Dose Level:	20mg ∨

Set event info, then click Submit: Cancel   Submit

Dose escalation method – Capping allows management of any time sensitive requirements between patient entry (24 hours between) and automatically closes the cohort and patient enrollment for groups, such as a Dose Escalation Committee, to review the data and determine how to proceed. It is important not to hard code any time sensitive requirements as they are often minimum time frames which must be adhered to and by allowing the end user to manage this manually, they can extend this period should additional time for evaluation be needed.

Number of patients per dose level – Capping of cohorts can allow the Sponsor to follow a typical 3+3 design where an initial cap of 3 is set. The cohort will automatically close after the first 3 patients are enrolled and create an automatic pause in enrollment while the Dose Escalation Committee can review the data and determine to edit the existing cohort cap to 6, open the next dose level, or stop the escalation completely via self-service controls. This capping functionality can continue to be used during the life of the study for any additional back filling of the escalation cohorts and balancing/limiting of expansion cohorts.

Maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) – Expansion Cohorts can be pre-built to allow for a dynamic selection of MTD/RP2D and dosing regimen for movement into Phase 2. There's an increased tendency to include as much in a single protocol as possible, such as Phase 1b/2 studies, where adjustable dose levels and dosing regimens on the cohort can allow dynamic entry from Phase 1b to Phase 2 based on the user controls.

Conclusion

Early phase studies may not have complex trial supply requirements but often need to be adaptable in their study design to pivot exploration in the direction the latest data suggests and this is where Veeva RTSM can provide great value on these studies. In the case of a dose escalation study, the right RTSM can provide study flexibility and oversight using dynamic, end-user controls over the patient management and dose exploration process, to bypass any 3rd party support and ensure a system can change and move at the pace the operations dictate. The solutions above are just an example of how Veeva RTSM can be adapted to meet the requirements of a protocol and its components which may need to be flexible and have end user controls.