

A Formal Dose Escalation/Safety Lead-In Request and Approval Process

M. Gawliu

UCSF Helen Diller Family Comprehensive Cancer Center

1. Background

Each year at UCSF, approximately 6,500 adults and children are newly diagnosed with cancer. The UCSF Helen Diller Family Comprehensive Cancer Center Data and Safety Monitoring Committee (HDFCCC DSMC) is responsible for ensuring participant safety and data integrity for all cancer related clinical research trials conducted at UCSF. For both Phase I and II trials, the DSMC monitors are tasked with monitoring source documents and conducting source document verification for participants in each dosing cohort prior to granting approval of enrollment in the next dosing cohort as per protocol. The HDFCCC DSMC has developed this distinctive dose escalation and safety lead-in review approval process that is unique to comprehensive cancer centers (CCCs).

2. Goals

- Provide improved oversight to ensure participant safety and data integrity
- Provide a streamlined process for the preparation/submission by the study team and the review/approval by the DSMC for all dose escalation and safety lead-in requests for applicable Phase I and II studies, respectively

3. Solutions and Methods

Two types of reviews are performed to ensure the safety of participants in their current cohort prior to moving to the next stage:

1. Dose escalation reviews prior to enrollment in the next higher dosing cohort
2. Safety lead-in reviews prior to opening the phase II study for further enrollment

These reviews verify that all participants in each dosing cohort are consented according to IRB regulations, meet all eligibility criteria, receive Investigational Product as per protocol, all serious adverse events and protocol violations are reported, and any undocumented dose-limiting toxicities are identified. In advance of a dose escalation/safety lead-in request, the study team communicates when the final participant of a cohort initiates treatment so the DSMC monitor can ensure the timely completion of monitoring the current cohort. Monitoring must be completed, and all significant safety issues addressed by the study team prior to the approval of the dose escalation/safety lead-in request to enroll in the next dosing cohort. Once monitoring concludes, the study team completes a Dose Escalation/Safety Lead-in Report that provides a summary of all safety data for the dosing cohort. The report is forwarded to the DSMC chair or vice chair for review and approval. Once approval is granted, the study team is formally notified that they may begin enrolling participants in the next dosing cohort. If approval is not granted, the reason for disapproval will be communicated to the PI with required action items (e.g., replacement of non-evaluable participants). Once these items have been addressed, the study team will then resubmit the amended Dose Escalation/Safety Lead-in Report for review and approval by the DSMC.

4. Outcomes

A novel, independent dose escalation/safety lead-in approval process improved data integrity and protocol compliance by identifying 4.1 percent of participants as non-evaluable and requiring

replacement per protocol definitions. This process was feasible with a turnaround time of approximately two business days from request to approval by the DSMC.

5. Lessons Learned and Future Directions

Future directions include refining dose escalation/lead-in approval request templates according to study phase/design, soliciting feedback from study teams across site committees, and benchmarking with other CCCs.

Figure

	Approved Safety Lead-Ins	Approved Dose Escalations	Approved Interim Analysis	Patients Reviewed
2020	3	2	1	34
2021	2	2	0	18
2022	1	5	0	21
Total Reviews	6	9	1	73