Agent Administration and Dosing Schemas

Study Treatment

- **Formatting:**
  - Use consistent naming (e.g. generic agent names vs. brand names).
  - Abbreviations must be initially accompanied by complete terminology.
  - Use consistent notation in expressing quantifiable units.
- **Calculations:**
  - If requesting a calculated value, please provide the formula.
- **Cycle (or Course) description:**
  - Specify the treatment cycle duration (or length).
  - Specify the cycle days on which each dose should be given in the treatment plan (e.g. days 1, 8, and 15 OR days 1-5).
  - Use "Day One" to indicate the first day of treatment. Use "Day 0" only as applicable (e.g., transplant studies).
  - Include specific starting days and times when appropriate. Use consistent time notation.
  - Include guidelines regarding "rounding-off" doses to the nearest capsule, tablet, or vial size or "capping" doses based on body surface area.
  - Oral administration:
    - Whenever possible, indicate whether agents should be administered (or taken) with food and explain dietary restrictions.
    - Describe ORAL agent dosages and schedules as the amount of agent that will be given (or taken) each time the agent is administered, not as a total daily dose that will be given (or taken) in divided doses, (e.g. 20 mg orally every 6 hours for 5 days vs. 80 mg per day, given in four divided doses for 5 days).

- **Treatment Modifications (Reduction/Escalation)**
  - Define the maximum number of allowable dose reductions before treatment must stop.
  - Include consistent descriptions of modifications among a study's treatment arms for the same agent.
  - Describe toxicity resolution requirements prior to treatment re-initiation or doses re-escalation.
  - Explain how modifications are to be handled during a cycle or at the start of the next cycle.
  - Specify whether agents can be modified independently.

- **Concomitant (Ancillary) Medications**
  - Clearly identified supportive care and essential ancillary medications required by a treatment regimen.
  - State complete instructions including appropriate indication, dosage, administration route, schedule, restrictions to use, and any other relevant data explicitly.
- **Treatment Assignment Unblinding**

Treatment and Schemas

There is no intention to un-blind individual patients at any time. Individual requests for urgent safety un-blinding require the approval of the Data Safety and Toxicity Committee (DSTC). The investigator may hold administration of study medications while waiting for a decision on un-blinding to be made. Approval may be obtained by contacting the DSTC directly during normal business hours. Upon approval by the DSTC, the appropriate staff member will break the blind (replace with the unblinding designee), and will provide the site with the patient's treatment assignment.

All unblinding communication must be documented by the site.

Examples of emergencies or circumstances that may require unblinding include:

- A life-threatening, unexpected AE that is thought to be related to agent X (investigational agent) and for which unblinding would change or influence treatment decisions
- Medication error, such as an accidental overdose leading to symptoms possibly secondary to the medication, that would warrant unblinding in order to more effectively manage toxicity
- Regulatory reporting requirement

EXAMPLES OF DOSING SCHEMA

State the starting dose of the agent and describe the dose escalation scheme and treatment regimen. Use exact doses rather than percentages.

Example:

DOSING SCHEMA			
Dose Level	**Agent X**	**Agent Y**	**Agent Z**
* Level -1	Dose and schedule	Dose and schedule	Dose and schedule
Level 1 [Starting Dose]	Dose and schedule	Dose and schedule	Dose and schedule
Level 2	Dose and schedule	Dose and schedule	Dose and schedule
Level 3	Dose and schedule	Dose and schedule	Dose and schedule
Level 4	Dose and schedule	Dose and schedule	Dose and schedule
Level 5	Dose and schedule	Dose and schedule	Dose and schedule
If appropriate for the study: *Level -1 will be explored if the starting dose is found to be too toxic.			

Investigators should also decide if intrapatient dose escalation is appropriate. This refers to subjects who are tolerating treatment at a lower dose level while the study is currently enrolling subjects to a higher dose level. Please be specific by making a statement advising the study team who will be responsible for making the decision. Example language is provided below:

Example: The Principal Investigator will determine if intrapatient dose escalation is appropriate on a case by case basis for the study.

Example: The Treating Physician will determine if intrapatient dose escalation is appropriate on a case by case basis for the study.

Example: No intrasubject dose escalation is allowed.

Agent Administration

Please state any special precautions or warnings relevant for agent administration (e.g. incompatibility of agent with commonly used intravenous solutions, necessity of administering agent with food, premedications, etc.).

Example

TREATMENT REGIMEN DESCRIPTION					
Agent	**Pre-medicate / Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Agent X	Pre-medicate with dexamethasone for 3 days **prior** to Agent X	300 mg/m^2 in 500 cc NS	IV over 2 hours **before** Agent Y	Week 1 Days 1-3	28 days
Agent Y	Avoid exposure to cold (food, liquids, air) for 24 hours after each dose	150 g/m^2 in 250 cc D5W	IV 1 hour **after** completion of Agent X through separate IV line	Week 1 Days 1-3	
Agent Z [a]	Take with food	**tablet	PO in the a.m.	Weeks 1+2, Daily	
***** Doses as appropriate for assigned dose level***					
[a] For orally administered agents, a method for assessing compliance with treatment should be included, i.e., **Suggested text is provided below:** [a] The subject will be provided a Subject Pill Diary [Appendix ____] and instructed in its use to record each dose of oral medication. ***Or place the statement under Section 6.1.1 as shown below.***					

EXAMPLES OF AGENT ADMINISTRATION NARRATIVE

Example of capsule/tablet: Subjects will receive [Agent X] mg/day orally on an empty stomach / with food in morning in 2 week (14 day) cycles. Subjects will be provided a Subject Pill Diary (Appendix _____) and instructed in its use to record each dose of oral medication.

Example of capsule/tablet: Name of Agent administration must be at least 1 hour before or after any other medications. An empty stomach is defined as at least 2 hours after the most recent food intake of any quantity and at least 1 hour before the next food intake. ***Note:*** "food intake" is better than "meal" as some may think a snack or smoothie is OK.

EXAMPLE: Agent Administration:
Subjects will receive modified [Agent X] on an outpatient basis on Day 1 of each 2 week (14 day) cycle. This regimen consists of concurrent IV administration of 85 mg/m^2 [Agent Y] and 400 mg/m^2 [Agent Z] over 120 minutes, followed by 400 mg/m^2 [Agent W] bolus, then 2400 mg/m^2 5-FU as a 46 hour infusion. Am ambulatory infusion pump may be used for the Agent W infusion. All subjects must have central intravenous access (e.g., Mediport, PICC line) for the continuous infusion of [Agent W].

EXAMPLE OF OTHER TREATMENT REGIMEN:

Example: Radiotherapy
Subjects on Arm A will receive treatment 5 days per week, in twice daily fractions, 1.5 Gy per fraction. The total dose will be 45 Gy in 30 fractions. There are no field reductions on this arm and a single PTV (PTV-1) will be used throughout the entire treatment. All fields must be treated daily and the entire PTV must be treated daily. The treatment plan will limit direct irradiation of the spinal cord during the afternoon treatment for the final 10 days of therapy. Radiation therapy (RT) commences on either day 1 of the first cycle of chemotherapy or day 1 of the second cycle of chemotherapy. There will be a minimum of 6 hours between the morning and afternoon fractions.

PHASE I SAMPLE SCHEMAS:

Example: Phase I Trial of [Agent X] and [Agent Y] for Relapsed or Refractory Hematologic Malignancies

STUDY SYNOPSIS
This study seeks to determine the maximum tolerated dose of [Agent X] given in conjunction with [Agent Y] in subjects with relapsed or refractory hematologic malignancies.

Eligible Subjects: Relapsed/refractory following at least one prior therapy for:
Non-Hodgkin Lymphoma (including cutaneous subtypes)
Hodgkin Lymphoma
Chronic Lymphocytic Leukemia
Chronic Myelogenous Leukemia
Multiple Myeloma

For phase 1 single-agent protocols:

Dose Escalation Schedule	
Dose Level	Dose of [Agent X]*
Level 1	
Level 2	
Level 3	
Level 4	
Level 5	
* *Doses are stated as exact dose in units* (e.g., *mg/m^2, mcg/kg, etc.) rather than as a percentage.*	

For phase 1 combination protocols:

Dose Escalation Schedule			
Dose Level	**Dose***		
	Agent X (units)	Agent Y (units)	Agent Z (units)
Level 1			
Level 2			
Level 3			
Level 4			
Level 5			
**Doses are stated as exact dose in units* (e.g., *mg/m^2, mcg/kg, etc.) rather than as a percentage.*			

EXAMPLE DOSE ESCALATION SCHEDULE

Dose-Escalation Schedule		
Dose Level	Dose	
	AGENT Y (25 mg/m^2/day)	AGENT X (mg/m^2 on day 1)
Level -1	3d	15
Level 1	5d	15
Level 2	5d	30
Level 3	5d	60
Level 4	5d	90
Level 5	5d	120

- 3 subjects will be entered sequentially to each dose level.
- Escalation will be determined by presence of dose-limiting toxicity (DLT), during the first treatment cycle. DLT involves select grade 3-4 non-hematologic toxicities or grade 4

hematologic toxicities.

- If none of the 3 subjects at a given dose level experience dose limiting toxicity (DLT) during the first cycle, dose escalation may proceed.
- If 1/3 experiences a DLT during the first cycle, 3 more subjects are treated at the same dose level. If only 1/6 experiences a DLT, dose escalation may proceed.
- If ≥2/6 experiences a DLT during the first cycle, no further subjects will be started at that dose. The MTD has been exceeded.
- The MTD is therefore defined as the dose level immediately **below** that at which ≥2/6 subjects experience a DLT.
- Following determination of the MTD, additional CLL/SLL subjects will be enrolled (if necessary), so that a total of 6 subjects with CLL/SLL will be treated at the maximum tolerated dose and 6 subjects are also treated at 1 dose level below the MTD.

Example:

TREATMENT REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Agent X	All subjects will receive dexamethasone 4 mg IC prior to each Agent X infusion. Premedicate with antiemetics as needed for subjects developing nausea or vomiting with a previous dose of Agent X	25 mg/m^2 in 500 ml NS or 500 ml 5% dextrose in water	IV infusion within 2 hours **after** _____ irradiation using non-DEHP lined administration sets.	Week Days Week 1 1,3,5 Week 2 8,10,12 Week 3 15,17,19 Week 4 22,24,26 Week 5 29,31,33	Weeks 1-5, Three times weekly
Agent Y	Increased oral intake of fluid should be encouraged 24 hours prior to administration; 1000 ml of ½ normal saline infused IV one hour prior before Agent Y. Premedicate with antiemetics as needed for subjects developing nausea or vomiting with a previous dose of Agent Y.	40 mg/m^2 diluted in 250 ml normal saline, reconstitution results in a colorless solution	IV infusion at a rate of 1 mg/min, usually infusing over 1 ½ hours (90 minutes) using **non-aluminum administration sets**; immediately following an additional 1000 ml of ½ normal saline infused over one hour.	Days 2, 9, 16, 23, 30	Weeks 1-5, Once weekly
_____ external beam radiation	Skin, antiemetics, or anti-diarrheal medications may be administered as needed.	1 80 cGy/day	See Section x.x	Weeks 1-5, Daily	Weeks 1-5, Daily (25 treatments)