Quality Assurance and Safety Monitoring Committee (QASMC)

Data and Safety Monitoring (DSM) Completion Instructions

May 2024

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BACKGROUND

Data and Safety Monitoring Requirements

In compliance with the Siteman Cancer Center Institutional Data and Safety Monitoring Plan, the Quality Assurance and Safety Monitoring Committee (QASMC) requires Data and Safety Monitoring (DSM) reports to be submitted on institutional trials as designated by the Protocol Review and Monitoring Committee (PRMC). A notification that the DSM report is due will be sent to the research team approximately 30 days before the due date. For studies requiring review by a Data and Safety Monitoring Board (DSMB), the DSM report will be reviewed first by the DSMB, after which the report plus the Board's findings will be submitted to QASMC as a DSMB report.

The first DSM/DSMB report is required either 30 days after the enrollment of the fifth participant (if sooner than 6 months after study activation) or 6 months after study activation (provided at least one patient has been enrolled; if zero patients have been enrolled at the 6-month mark, the first report will be required one year after accrual opens provided at least one patient has been enrolled). The frequency of subsequent reports is dictated by the protocol with the last report due 6 months after the last patient has completed treatment.

Given the importance of timely review, **accrual will be suspended** to those studies where the DSM/DSMB report is overdue by more than 120 days. Reminders and requests for information are sent regularly after the due date. If the report is not received within 120 days of its due date, a notice will be sent to the Washington University IRB, PRMC, and research team, as well as to the NCI Program Director responsible for funding the trial (if applicable). The Washington University IRB will notify the OHRP and FDA (if applicable) in accordance with the requirement that all suspensions and closures be reported to these agencies. Once the DSM/DSMB report is received and approved by the QASMC, notice will be sent to resume the study.

REQUIRED INFORMATION IN DSM REPORTS

DSM Report Documentation

Single Institution Studies

DSM reports are to be prepared by the research team and reviewed/signed/dated by the PI and statistician.

The DSM report is generated from OnCore (Reports/Safety Monitoring/Custom Reports/DSM Report 07 31 2022) and some information in the report is auto-populated using information present for the study record in OnCore. **Many institutional studies contain study-specific DSM tables as an appendix to the protocol; those tables are customized for the study and are to be used in lieu of the blank tables in the DSM report template.** A Word version of the study protocol should be downloaded from myIRB so that the tables can be completed. The corresponding blank tables in the DSM report template should be deleted; the study-specific tables may be pasted

directly into the DSM report (if possible) or sent as a single supplemental PDF (if formatting difficulties arise).

All relevant information should be provided but at a minimum, reports must include the following items:

- Study demographic information (local protocol number, title, report date, list of primary study team members, study sites, primary sponsor and secondary sponsors, phase, IND/IDE status, date of most recent QA audit, and study status history (including activation and suspension dates)
- Accrual information, including study-wide target accrual and actual accrual, anticipated and/or actual accrual end date, and accrual by year by site (if applicable)
- Subject status information presented in both cumulative format (total number of subjects who consented, enrolled, screen failed, started intervention, discontinued intervention, went off study, expired) and current format (number of subjects in screening, on intervention, in follow-up or off study at time of report)
- Protocol objectives and the number of participants who are evaluable for each objective
- History of study (including summaries of substantive amendments, accrual suspensions and reasons, protocol exceptions, errors, and breaches of confidentiality)
- Summary of exceptions, noncompliance reports, and unanticipated problems reported to the IRB
- Early stopping rules and data describing whether the stopping rules have been met (if applicable)
- Interim analysis plans and the results of the interim analysis (if applicable)
- Separate serious adverse event (SAE) and worst grade toxicity tables, each separated by arm/cohort/dose level (if applicable)
- Participant-level response and survival data by arm/cohort/dose level (if applicable)
- Summary of specimen collection (percentage of participants who have had specimens collected at each required time point)
- Abstract submissions or publications
- Summary of recent literature that reports developments that may affect the safety of participants or the ethics of the study
- PDF copy of current HRPO-approved consent form(s)
- PDF copy of current HRPO-approved protocol

<u>Multi-site Institutional Studies Where WU is the Coordinating Center</u>

Reports should include all relevant information as detailed above, incorporating data from all study sites including the cover sheet with the decision of the DSMB meeting signed by the DSMB members.

For studies that are using the Siteman Standing DSMB, the DSM report and all applicable documents will need to be submitted by the team to the DSMB first. Upon receipt of the DSMB's determination, the study team is responsible for submitting all documentation (including DSMB outcomes letter) to QASMC for its review.

Blinded Studies

The study statistician is responsible for preparing the unblinded data for submission to the DSMB. The statistician must email the unblinded data tables directly to QASMC without including any study team members on the email in order to maintain the blind. The study team should send the finalized blinded DSM report to the statistician so the statistician can verify that the DSM report and the unblinded data report match. The statistician should not specifically name the arms (such as experimental and placebo) but instead assign an arm number (such as Arm 1 and Arm 2).

CTEP Studies

For CTEP studies where a WU investigator is the study chair and the protocol requires local data and safety monitoring (typically for phase I of a phase I/II study), the Siteman Standing DSMB will serve as the study's DSMB and the standard DSM report template out of OnCore may be used. Because the data required for the report tables is not all present in OnCore for CTEP studies, the research team will need to work with the study statistician, participating sites, and data coordinating center to obtain all required information. QASMC does not review DSM reports for CTEP studies after DSMB review.

DSM REPORT INSTRUCTIONS

Demographics

The below Demographic table pulls from OnCore into the DSM report for the study. Please review the following fields for accuracy, and if changes are needed, please update both the report and the corresponding fields in OnCore:

1. The Principal Investigator, Statistician, Primary Clinic Coordinator, Primary Data Coordinator, and Primary Regulatory Coordinator fields are fed by the Staff tab located in the PC Console/Main tab for the study.
2. The Study Sites field is fed by the Institution tab in PC Console for the study. Please make sure all participating sites are listed.
3. The Primary and Other Sponsor(s) fields are fed by the Sponsor tab located in the PC Console/Main tab for the study. Please make sure that the sponsors listed in myIRB match the sponsors listed in OnCore.

HRPO #:	202512035	**Title:**	Sample Study		
Report Date:	04/25/2023	**Principal Investigator:**	Seinfeld, Jerry	**Statistician:**	Benes, Elaine
Primary Clinic Coordinator:	Costanza, George	**Primary Data Coordinator:**	Whatley, Tim	**Primary Regulatory Coordinator:**	Ross, Susan
Study Sites:	Memorial Sloan-Kettering				
Primary Sponsor:	Washington University		**Other Sponsor(s):**	National Cancer Institute, Pfizer	
Phase:	I/II	**IND / IDE:**	N	**Date of recent QA audit:**	12/13/2022

Study Status History

The below Study Status History table pulls from OnCore into the DSM report for the study. The data for this table comes from the Status tab in PC Console. Prior to submitting the DSM report to QASMC, please make sure that the study statuses of suspended and closed to accrual have a change reason noted in OnCore. The change reason feeds the details fields in this table.

Study Status History		
Status Date	**Status**	**Details**
12/11/2012	OPEN TO ACCRUAL	
01/02/2014	SUSPENDED	Cohort Filled
02/14/2014	OPEN TO ACCRUAL	
10/23/2020	SUSPENDED	Cohort Filled
01/07/2021	CLOSED TO ACCRUAL	Accrual goal met

Accrual Summary

The below Accrual Summary table pulls from OnCore into the DSM report for the study.

Accrual Summary			
Study-wide target accrual	80	**WU target accrual**	15
Total accrual to date	56	**WU accrual to date**	10
WU activation date	12/11/2012	**Expected accrual completion date**	05/11/2022
		Date of closure to accrual	01/07/2021

- Study-wide target accrual pulls from Protocol Target Accrual field (PC Console/Main tab/Accrual Information table).
- Total accrual to date pulls from the number of participants that are listed in the Accrual tab.
- WU activation date pulls from the first open to accrual date located in the Status tab.
- WU target accrual pulls from the RC Total Accrual Goal (Lower) field (PC Console/Main tab/Accrual Information table).
- WU accrual to date pulls from the participants that have a study site associated with WU that are listed in the Accrual tab.
- Expected accrual completion date is calculated by adding the Accrual Duration (Months) field (PC Console/Main tab/Accrual Information table) to the open to accrual date located in the Status tab.
- Date of closure to accrual pulls from the last closed to accrual date listed in the Status tab. This will be blank if the study has not closed to accrual.

Please review all fields for accuracy prior to submission of the DSM report to QASMC. Pay specific attention to the following:

1. Confirm that all participants have been enrolled in OnCore (so that the accrual to date fields are correct).
2. If the study has participating sites, please make sure that the Affiliate Accrual Goal field (PC Console/Main tab/Accrual Information table) is completed, and that the RC Total Accrual Goal (Lower) field plus the Affiliate Accrual Goal field equals the Protocol Target Accrual field.
3. If the Expected accrual completion date is in the past or if the Expected accrual completion date is within the next 6 months, contact the PI to find out a revised expected accrual completion date. Insert the correct date in the DSM report and update OnCore as follows:
    a. Update the Accrual Duration (Months) field so that the first open to accrual date + the accrual duration in months = the new expected accrual completion date.
    b. Update the RC Annual Accrual Goal field to provide an updated estimate of number of patients to be enrolled per year.
        i. Calculation for RC Annual Accrual Goal for single institution study: Protocol Target Accrual / Accrual Duration (Months) = # estimated to be accrued per month. Multiply this number by 12 to get the RC Annual Accrual Goal.
        ii. Calculation for RC Annual Accrual Goal for multiple institution study: RC Total Accrual Goal (Lower) / Accrual Duration (Months) = # estimated to accrued per month. Multiply this number by 12 to get the RC Annual Accrual Goal.

Accrual by Year

The below Accrual by Year table pulls from the participants listed in the Accrual tab sorted by On Study date year. The numbers in the Annual actual accrual column, when added up, should total the number of patients enrolled to date.

Accrual by Year		
Year	**Annual actual accrual**	**Cumulative accrual**
2013	6	6
2014	5	11
2015	7	18
2016	9	27

Cumulative Subject Status by Arm

The below Cumulative Subject Status table pulls from the information that is listed in the Accrual tab. This table may require updates by the study team to make sure all data in the table is clear and precise.

Cumulative Subject Status by Arm										
Arm	Dose level	Total subjects who.....								
		Consented to study	Enrolled to study	Screen failed	Went on treatment	Went off treatment	Went off study	Expired	Expired while on treatment	Expired while in follow up
Escalation Cohort	Epacadostat 300 mg	20	4	6	4	4	0	0	0	0
Escalation Cohort	Epacadostat 400 mg		4		4	2	0	0	0	0
Escalation Cohort	Epacadostat 600 mg		6		6	6	0	0	0	0
Unassigned Arm	Screening		0	0	0	0	0	0	0	0

- All arms/cohort/groups/dose levels should be represented in the table with an individual row.
- The designation “unassigned arm” can be used for randomized trials where the patient has not yet been randomized.
- The Consented to study column needs to match the Total Consented field that can be located in the Accrual tab in OnCore.
- The Enrolled to study column needs to match the Accrual to Date number that is listed in the PC Console in OnCore. A participant is considered enrolled if they have an On Study date in OnCore.
- The Screen failed column should equal the number that is in the Consented to study column minus the number(s) in the Enrolled to study column and minus the Currently in screening column in the Current Subject Status by Arm table. The Screen failed column is a catchall and should include participants who were found ineligible, withdrew, expired, or the treating physician decided the participant should not be enrolled in the study.
- There may be instances where a participant has enrolled but did not start treatment. In these instances, this participant will be NOT be considered a screen failure but will instead be counted in the Enrolled to study column (as they will have had an On Study date in OnCore) and will not be counted in the Went on treatment column (as they will not have had an On Treatment date). They will also be counted in the Went off study column. For clarity, add an asterisk next to the number in the Enrolled to study column and then include a note at the bottom of the table stating the number of participants who enrolled but did not start treatment, and include the reason the participant(s) did not start treatment.
- The Went on treatment column should match the number of participants who have an On Treatment date in OnCore. If the participant did not start treatment, then they should not have an On Treatment date in OnCore and they would not be counted in the Went on treatment column in this table. For studies without a treatment component, the participants enrolled to the study would not have On Treatment dates in OnCore and there should not be any numbers listed in the Went on treatment column.

- The Went off treatment column should match the number of participants who have both On Treatment and Off Treatment dates in OnCore. Patients who never started treatment should not have an Off Treatment date in OnCore. If the study does not have a treatment component, then none of the patients should not have an Off Treatment date in OnCore and there should not be any numbers listed in the Went off treatment column.
- The Went off study column should match the number of participants in OnCore who have an Off Study date in OnCore.
- The Expired column includes all participants who were enrolled in the study and expired. This includes participants who expired after their off-study date.
- The Expired while on treatment column should match the number of participants who have an expiration date in OnCore that is between the On Treatment date and the Off Treatment date in OnCore. If the study does not have a treatment component then there should not be any numbers listed in the Expired while on treatment column.
- The Expired while in follow up column should match the number of participants who have an expiration date in OnCore that is between the Off Treatment date and Off Study date in OnCore for studies that have a treatment component. If the study does not have a treatment component then this column should match the number of participants who have an expiration date in OnCore that is between the On Study date and the Off Study date in OnCore.
- Off Study dates in OnCore should not be later than the Expired date in OnCore.
- To make sure the numbers in this table all add up, the study team should do the following:
    - Verify that the Enrolled to study column and the Screen failed column adds up to the number in the Consented to study column (unless there are patients who have consented and are in screening but haven't enrolled yet; those patients should show up in the Currently in screening column in the Current Subject Status by Arm table). Add notes to the Screen failed column if there are participants who had another reason for not enrolling in the study (such as withdrawal of consent, rapid disease progression, moved out of state, etc.).
    - Verify for each individual row that the Went on treatment column + Went off treatment column + Went off study column = Enrolled to study column.
- If the study team provides extra tables for the DSM report that contains On Study, On Treatment, Off Treatment, Off Study, or Expiration dates, these tables need to match what is in OnCore and what is in this table. All tables and OnCore need to be consistent.
- For studies that have participating sites, please check with secondary sites about patient statuses (as those are not always kept current).
- Additionally, for studies that have participating sites, please check the Follow-up tab in the Subject Console for dates of subject expiration, as there is an expired date field that participating sites sometimes complete when a subject dies. This date does <u>NOT</u> feed into field in the Accrual tab that indicates date of death for a participant, nor does it feed into the DSM report. The study team will need to contact OnCore support to get the date of death to feed properly into the Accrual tab in PC Console.

Current Subject Status by Arm

The below Current Subject Status by Arm table pulls from the information that is listed in the Accrual tab. This table may require updates by the study team to make sure all data in the table is clear and precise.

Current Subject Status by Arm					
Arm	**Dose level**	**Currently in screening**	**Currently receiving intervention**	**Currently in follow-up**	**Currently off study or expired**
Escalation Cohort	Epacadostat 300 mg	0	0	4	0
Escalation Cohort	Epacadostat 400 mg	0	2	2	0
Escalation Cohort	Epacadostat 600 mg	0	0	5	1
Unassigned Arm		2	0	0	0

- All arms/cohort/groups/dose levels should be represented in the table with an individual row.
- The designation "unassigned arm" can be used for randomized trials where the patient is in screening and has not yet been randomized.
- The Currently in screening column should include those participants who signed consent and who are in the screening process or about to start the screening process.
- The Currently receiving intervention column should match the number of participants who have an On Treatment date, no Off Treatment date, and no Off Study date in OnCore.
- The Currently in follow-up column should match the number of participants who have an On Treatment date, an Off Treatment date, and no Off Study date in OnCore for studies with a treatment component. For studies without a treatment component, this column should match the number of participants with an On Study date and no Off Study date in OnCore.
- The Currently off study or expired column should match the number of participants who have an On Study date, On Treatment date, Off Treatment date, and Off Study date in OnCore for studies with a treatment component. For studies without a treatment component, this column should match the number of participants with an On Study date and Off Study date in OnCore.
- To make sure the numbers in this table all add up, the study team should do the following:
    - For studies with a treatment component, verify that the Currently receiving intervention column equals the number of participants who are currently receiving treatment. To make sure this column is in harmony with the Cumulative Subject Status by Arm table, this number should equal the following: Went on treatment column – Went off treatment column = Currently receiving intervention.
    - For studies without a treatment component, the Currently receiving intervention column should be listed as zero for each individual row.

- To make sure that the Currently in follow-up column is in harmony with the Cumulative Subject Status by Arm table, this number should equal the following: Went off treatment column – Went off study column = Currently in follow-up.

Example using the following tables:

Cumulative Subject Status by Arm										
Arm	Dose level	Total subjects who.....								
		Consented to study	Enrolled to study	Screen failed	Went on treatment	Went off treatment	Went off study	Expired	Expired while on treatment	Expired while in follow up
Escalation Cohort	Epacadostat 300 mg	20	4	6	4	4	0	0	0	0
Escalation Cohort	Epacadostat 400 mg		4		4	2	0	0	0	0
Escalation Cohort	Epacadostat 600 mg		6		6	6	0	0	0	0
Unassigned Arm	Screening		0	0	0	0	0	0	0	0

Current Subject Status by Arm					
Arm	Dose level	Currently in screening	Currently receiving intervention	Currently in follow-up	Currently off study or expired
Escalation Cohort	Epacadostat 300 mg	0	0	4	0
Escalation Cohort	Epacadostat 400 mg	0	2	2	0
Escalation Cohort	Epacadostat 600 mg	0	0	5	1
Unassigned Arm		2	0	0	0

1. In the Cumulative Subject Status table, the Escalation Cohort Epacadostat 300 mg arm and dose level shows:
    a. 4 participants were enrolled.
    b. 4 participants went on treatment.
        i. With 4 enrolled and 4 on treatment, the number currently in screening should be 0 (which matches the Current Subject Status table).
    c. 4 participants went off treatment.
        i. With 4 on treatment and 4 off treatment, the number currently receiving intervention should be 0 (which matches the Current Subject Status table).
    d. 0 participants went off study.
        i. With 4 off treatment and 0 off study, the number currently in follow-up should be 4 (which matches the Current Subject Status table).

ii. With 0 off study, the number currently off study or expired should be 0 (which matches the Current Subject Status table).

2. In the Cumulative Subject Status table, the Escalation Cohort Epacadostat 400 mg arm and dose level shows:
    a. 4 participants were enrolled.
    b. 4 participants went on treatment.
        i. With 4 enrolled and 4 on treatment, the number currently in screening should be 0 (which matches the Current Subject Status table).
    c. 2 participants went off treatment.
        i. With 4 on treatment and 2 off treatment, the number currently receiving intervention should be 2 (which matches the Current Subject Status table).
    d. 0 participants went off study.
        i. With 2 off treatment and 0 off study, the number currently in follow-up should be 2 (which matches the Current Subject Status table).
3. In the Cumulative Subject Status table, the Escalation Cohort Epacadostat 600 mg arm and dose level shows:
    a. 6 participants were enrolled.
    b. 6 participants went on treatment.
        i. With 6 enrolled and 6 on treatment, the number currently in screening should be 0 (which matches the Current Subject Status table).
    c. 6 participants went off treatment.
        i. With 6 on treatment and 6 off treatment, the number currently receiving intervention should be 0 (which matches the Current Subject Status table).
    d. 0 participants went off study.
        i. With 6 off treatment and 0 off study, the number currently in follow-up should be 6 (which <u>does not</u> match the Current Subject Status table, which shows 5 in currently in follow-up).
            1. Either update the Went off study column to 1 in the Cumulative Subject Status table or update the Currently in follow-up column to 6 and the Currently off study or expired column to 0 in the Current Subject Status table. Subject statuses in OnCore for patients in this arm and dose level should be double-checked to make sure all relevant dates are entered.
4. In the Current Subject Status table, the Unassigned arm row shows that there are 2 participants who are currently in screening.
    a. To double-check this with the Cumulative Subject Status by Arm table, you would add the number in the Went on treatment column(s) to the number in the Screen failed column and then subtract that number from the number in the Consented to study column.
        i. For this example, the Consented to study column is 20, the Went off treatment column(s) is 14, and the Screen failed column is 6. The math would be 20-(14+6) = 0.
        ii. However, because the Current Subject Status table shows that there are 2 participants in screening, the study team needs to determine which subject statuses in OnCore are incorrect and make corrections both to the appropriate cells in the table and to the statuses in OnCore as needed.

Site Status and Accrual

The below Site Status and Accrual table pulls from the information that is listed in the Institution tab. Please review the following fields for accuracy, confirming that all participating sites are included, and if changes are needed, please update both the report and the corresponding fields in OnCore. This table should match the data in OnCore and OnCore should be up-to-date as of the day of the report.

Site Status and Accrual					
Site name	**Date of site activation**	**Current site status**	**Total site accrual**	**If closed to enrollment, date**	**If fully closed, date**
Washington University in St. Louis	01/18/2022	OPEN TO ACCRUAL	9		
Dana Farber Cancer Institute	01/12/2023	OPEN TO ACCRUAL	1	08/08/2023	

Protocol Objectives and Subject Evaluability

This table needs to be completed manually by the study team. If there is an appendix to the protocol containing study-specific DSM tables, this table will be included and should be pasted into the report in place of this table (preferred) or inserted as an appendix to the DSM report with the template table indicating page # (if formatting problems preclude directly pasting the table into the report).

- Delete the red text/row in the template.
- This table should include all primary, secondary, exploratory, tertiary, and correlative objectives present in the Objectives section of the protocol. If there are inconsistencies between the objectives as listed in the protocol summary, objectives section, and statistical section, it is recommended that a protocol amendment be submitted.
- Sometimes objectives have more than one endpoint. If that is the case, the column reporting the # of patients evaluable for the endpoint to date will need to include how many patients are evaluable for each endpoint.
- For guidance on how to determine the number of subjects evaluable for each endpoint, refer to the protocol section defining evaluability (if present) or to the statistical section.
- The study statistician must review this table to determine the accuracy of the numbers listed. It is recommended that the coordinator completing the report bring this to the statistician's attention at the time of review.

Example below:

Protocol Objectives and Subject Evaluability		
Type of objective (primary, secondary, exploratory, etc.)	**Objective**	**# of patients evaluable for the endpoint to date**
Primary	To determine the overall response rate to treatment with the regimen	20
Secondary	To assess safety and tolerability of the combination of the regimen including acute toxicities and late toxicities	Acute = 20 Late = 18
Secondary	To assess the clinical efficacy of the combination of the regimen including progression-free survival, duration of response, and overall survival.	PFS = 20 DoR = 20 OS = 20
Exploratory	To explore potential association between anti-tumor activity and pharmacodynamics effects with both blood and tissue.	Blood = 20 Tissue = 19

Protocol History

This table pulls from the IRB review tab.

- Delete the red text/row in the template.
- Remove minor modifications such as study team changes (excepting PI changes).
- Add a description for all amendments where one doesn't pull from OnCore.

Example below:

Protocol History		
Type of Submission	**Date of IRB approval**	**Summary**
Modification	03/09/2023	Changed PI from Jerry Seinfeld to Elaine Benes.
Continuing Review	01/21/2023	
Modification	01/21/2023	Added a new exploratory objective.
Initial Review	11/04/2022	

Summary of Exceptions, Noncompliance Reports, and Unanticipated Problems

This table needs to be completed manually by the study team.

- Delete the red text/row in the template.
- This table should include each REF approved or acknowledged the HRPO. If none have occurred to date, then indicate that in the table.
- If multicenter, include for ALL participating sites.

Example below:

Summary of Exceptions, Noncompliance Reports, and Unanticipated Problems		
Type of event	**Event date**	**Event description**
Exception	01/22/2023	Patient's screening CT will be out of the protocol required time frame by 2 days.
Noncompliance	01/24/2023	Patient's daily medication included metformin and that is an excluded medication per the protocol eligibility criteria. The patient started treatment while still taking metformin.

Interim Analysis and Early Stopping Rules

This table needs to be completed manually by the study team in collaboration with the statistician. If there is an appendix to the protocol containing study-specific DSM tables, this table will be included and should be pasted into the report in place of this table (preferred) or inserted as an appendix to the DSM report with the template table indicating page # (if formatting problems preclude directly pasting the table into the report).

- Delete the red text/row in the template.
- If the study contains an interim analysis and/or early stopping rules, they will be found in the protocol. Generally, they can be found in the statistical section of the protocol but may also be found elsewhere.
- It is imperative that both the study statistician and the study principal investigator review the results of the interim analysis and the early stopping rules for accuracy.
- If the study has a required Interim Analysis and the analysis has been completed, provide a summary narrative addressing all aspects of the Interim Analysis. A summary table is helpful to include as well. See example below.
- If the study has Early Stopping Rules, indicate whether any of the stopping rules have been met and provide a table containing data justifying your response. See example below.

Example below:

Interim Analysis and Early Stopping Rules

Does the study design include an interim analysis?	X	Yes		No

If yes, please insert text describing interim analysis from the protocol:
In the first stage of the trial, 10 patients will be enrolled. If five or fewer patients have an objective tumor response (complete response or partial response), study will be stopped and the alternative hypothesis will be rejected. Otherwise, 20 additional patients will be enrolled for a total of 30 patients.

If yes, has interim analysis been conducted as of the date of this report?	X	Yes		No

If yes, please insert results of interim analysis:
In the first 10 patients enrolled, 6 patients had an objective tumor response which meets the criteria to continue. It was determined that the study could proceed to stage 2.

Patient ID#	Best Response	Order Enrolled
001	PR	1st
003	CR	3rd
004	PR	4th
007	PR	8th
008	PR	7th
010	CR	10th

Are there early stopping rules that outline circumstances under which the study must be suspended or closed?	X	Yes		No

If yes, please insert text describing early stopping rules from the protocol:
Two cohorts will be pooled together for safety monitoring. Early stopping of this trial is calculated based upon the report of study treatment-related grade 3 or greater adverse events. A Bayesian safety monitoring plan will be implemented once the first 10 evaluable patients are available. A Bayesian sequential safety monitoring will be defined as $Pr(\theta T > \theta 0 \mid data) > 0.80$, where θT denotes the proportion of toxicity and $\theta 0$ ($\theta 0$=20%) represents the rate under null hypothesis (maximum probability of toxicity allowed). That is, enrollment will be stopped early whenever there is >80% chance that the event rate is larger than the null. The trial will be recommended to stop for excessive toxicities if: 4 or more patients experience toxicity in first 10 patients, 6 or more patients experience toxicity in first 20 patients, or 8 patients experience toxicity before the last patient (30^{th}) is enrolled.

If yes, please provide data describing whether any patients have met the stopping rules: The study has not met the stopping rules to date.

Patient ID#	Adverse Event	Attribution to Study Treatment	Order Enrolled
001	Grade 4 neutropenia	Possibly	1^{st}
006	Grade 3 AST	Probably	6^{th}
020	Grade 4 dyspnea	Possibly	20^{th}
022	Grade 5 sepsis	Probably	22^{nd}

Serious Adverse Events (SAEs)

This table is pulled from SAEs that are entered into the SAE tab in OnCore.

- If OnCore is not used to track SAEs, then this table will need to be manually completed.
- The SAE table must be separated by arm/cohort/dose level (if applicable).
- All SAEs that meet the definition found in 21 CFR 312.32 are included. This includes SAEs that are not reportable to HRPO or the FDA (e.g. SAEs that are not SUSARs).
    - If an AE is flagged as an SAE **only** by selecting the checkbox on the AE log page and is not entered in the SAE tab in OnCore, it will not pull to this table and will need to be manually added to the table (or added to the SAE tab before the report is run).
- Because SAEs are, by definition, adverse events, all SAEs should also be present in the Worst Grade Toxicity (Adverse Event) tables.
    - If an SAE is not present in the AE/Toxicity CRF, it will not show up in the Worst Grade Toxicity table.
- If the SAE is listed as an "Other" adverse event, please be sure to list the specific adverse event. For example, if the SAE is for COVID-19 infection, it is pulled into the DSM report as "Infections and infestations – Other, specify." Revise the SAE to state "Infections and infestations – Other, specify – COVID-19."

Example below:

SAEs						
Subject arm	Escalation and Expansion: APL101 + Osimeritnib					
Dose level	Dose Escalation: Level 1 300 mg PO APL-101 + Osimertinib					
UPN	**Subject site**	**Event**	**Grade**	**Attribution**	**Event date**	**Hospitalization**
01-004	WUSM - Washington University School of Medicine	Pneumothorax	3	InvTx: Unrelated Drug: APL-101: Unrelated Drug: osimertinib (Tagrisso): Unrelated	08/29/2022	N
Subject arm	Escalation and Expansion: APL101 + Osimeritnib					
Dose level	Dose Escalation: Level 1 600 mg PO APL-101 + Osimertinib					
UPN	**Subject site**	**Event**	**Grade**	**Attribution**	**Event date**	**Hospitalization**
01-009	WUSM - Washington University School of Medicine	White blood cell decreased	4	InvTx: Unrelated Drug: APL-101: Unrelated Drug: osimertinib (Tagrisso): Unrelated	01/19/2023	Y

Worst Grade Toxicity (by Arm)

If OnCore is used for data entry and the standard AE form is used (AE-001 v4), the Worst Grade Toxicity table will be pulled from the eCRFs in OnCore. If a study-specific AE form is used, the Worst Grade Toxicity Table will need to be completed manually. If REDCap is used for data entry, the Worst Grade Toxicity table can be generated out of REDCap; the DSM notification email contains a link to a request form with instructions on how to request this table. It will need to be manually added to the DSM report. If other databases or paper CRFs are used, the table will need to be completed manually and then manually added to the DSM report. If manual table creation is needed, it can be downloaded from the QASMC website: https://siteman.wustl.edu/research/resources-for-researchers/qasmc-forms/.

- Delete the red text/row in the template.
- The worst grade toxicity table must be separated by arm/cohort/dose level (if applicable). This applies to phase I studies with different dose levels, randomized studies with different arms, or studies with multiple cohorts.
- The number of patients evaluated for toxicity as of the report date must be added manually. If the table is split by arms/cohorts/dose level, then the number of patients evaluated for toxicity as of the report date needs to be listed for each table.
- Verify that only the worst grade toxicity experienced by participant is listed in the table.
- Verify that there are not more instances listed per adverse event than there are patients who were evaluated for toxicity.
- Verify that there are not redundant adverse event rows.
- Verify that each adverse event is listed under the appropriate System Organ Class.
- Verify that the SAE and the corresponding AE are named consistently.
- Group system organ classes together.
- Be sure to include a description for any grade 5 events in the G5 description column.

Example below:

Worst Grade Toxicity (by Arm)								
Arm	Escalation and Expansion: APL101 + Osimeritnib	**How many patients in this arm were evaluated for toxicity as of this report date?**	5					
Dose level	Dose Escalation: Level 1 300 mg PO APL-101 + Osimertinib							
System organ class	**CTCAE term**	**Other**	**G1**	**G2**	**G3**	**G4**	**G5**	**G5 description**
Blood and lymphatic system disorders	Anemia		2	0	0	0	0	

Eye disorders	Blurred vision		1	0	0	0	0	
Gastrointestinal disorders	Nausea		1	0	0	0	0	
Gastrointestinal disorders	Vomiting		1	0	0	0	0	

Arm	Escalation and Expansion: APL101 + Osimeritnib	**How many patients in this arm were evaluated for toxicity as of this report date?**	2
Dose level	Dose Escalation: Level 2 400 mg PO APL-101 + Osimertinib		

System organ class	CTCAE term	Other	G1	G2	G3	G4	G5	G5 description
Blood and lymphatic system disorders	Anemia		1	0	0	0	0	
Ear and labyrinth disorders	Ear pain		0	0	1	0	0	
Eye disorders	Eye disorders - Other, specify	edema - intermittent	1	0	0	0	0	
Gastrointestinal disorders	Constipation		1	0	0	0	0	
General disorders and administration site conditions	Edema limbs		1	0	0	0	0	

Response and Survival (by Arm)

Some of the data for this table is pulled directly from OnCore such as On Tx date and vital status. The remaining information needs to be manually added by the study team. If there is an appendix to the protocol containing study-specific DSM tables, this table will be included and should be pasted into the report in place of this table (preferred) or inserted as an appendix to the DSM report with the template table indicating page # (if formatting problems preclude directly pasting the table into the report).

- Delete the red text/row in the template.
- The auditor who performs the pre-review on the initial DSM table may request that certain columns be added or certain columns be deleted. This is to tailor this table to the study.
- Make a separate table for each arm/cohort/dose level if applicable.
- Mark N/A for fields that do apply.

Example below:

Response and Survival (by Arm)								
Arm	Escalation and Expansion: APL101 + Osimeritnib							
Dose level	Dose Escalation: Level 1 300 mg PO APL-101 + Osimertinib							
UPN	**Subject site**	**On tx date**	**# cycles complete**	**Pt replaced**	**DLT**	**Best response**	**Off tx reason**	**Vital status**
01-001	WUSM - Washington University School of Medicine	04/12/2022	8	No	No	CR	N/A, still on treatment	alive
01-002	WUSM - Washington University School of Medicine	03/03/2022	<1	Yes	N/A	NE	Other (Patient Choice)	alive
01-003	WUSM - Washington University School of Medicine	03/22/2022	6	No	No	SD	N/A, still on treatment	alive

Summary of Specimen Collections

This table needs to be completed manually by the study team. If there is an appendix to the protocol containing study-specific DSM tables, this table will be included and should be pasted into the report in place of this table (preferred) or inserted as an appendix to the DSM report with the template table indicating page # (if formatting problems preclude directly pasting the table into the report).

- Delete the red text/row in the template.
- Add one row per type of specimen at each time point by referring to the study calendar and/or the correlatives section of the protocol. If there are discrepancies between these sections (or between the protocol and the consent form), it is recommended that a protocol amendment be submitted.
- Do not provide individual-level data.
- Make sure to complete the # of patients eligible for collection at each time point.
- Make sure to complete the % of patients who have reached this time point and had the specimen collected and verify that the math is accurate. For example, if there was a Cycle 1 Day 1 peripheral blood collection and 10 patients were eligible for collection at this time point but only 8 patients had the sample collected, then the % of patients who have reached this time point and had the specimen collected would be 80%.

Example below:

Summary of Specimen Collections			
Type of specimen	**Time point**	**# of patients eligible for collection at this time point**	**% of patients who have reached this time point and had the specimen collected**
Tissue	Baseline	10	100%
Peripheral blood – ctDNA	Baseline	10	100%
Tissue	C1D15	10	90%
Peripheral blood – ctDNA	C1D15	10	90%
Peripheral blood – PKs	C2D1	9	100%

Signatures of the Principal Investigator and Statistician

- The Principal Investigator of the study needs to sign and date the DSM report.
- The Statistician of the study needs to sign and date the DSM report. The Statistician needs to be sent the DSM report no later than 1 week prior to the submission deadline.
- QASMC will accept a scanned copy of the handwritten signature and date or a DocuSign signature and date for both the Principal Investigator and the Statistician.

HELPFUL HINTS

- **Start early.**
- The data contained in the DSM report must be accurate within 30 days of submission to QASMC. If the study has an internal DSMB or a standing DSMB, the data must be accurate within 30 days of review by the DSMB. It is assumed that the date in the first table of the DSM report is the data cut-off date – the report must be current up to that date, and it must not contain information that occurred after that date.
- Generate a DSM report from OnCore for each DSM report submission. Do not revise an older DSM report for submission.
- Any questions about DSM reports can be emailed to qasmc@wustl.edu prior to pre-review.
- **Turn the DSM report in on time.**
    - It is permissible to send the report to qasmc@wustl.edu prior to obtaining signatures for review by the pre-reviewer. Send the report at least 10 days prior to the due date. Note that when requesting review prior to obtaining signatures, all items should be addressed with the pre-reviewer PRIOR to final signature and submission of the report to QASMC.
- If the DSM report will be late, email qasmc@wustl.edu to request an extension.
- Verify that OnCore data matches the DSM report data.
- Check the DSMB/Standing DSMB outcomes letter for any changes that may be required prior to submitting to QASMC for review.
- **Review the correspondence from the previous DSM report pre-review so that the same issues are not noted on the current DSM pre-review.**
- Be sure to include all required documents in the email to QASMC:
    - Signed DSM Report (PDF)
    - Any supplementary tables containing data for the primary or secondary objectives (PDF)
    - Current HRPO-approved protocol (PDF)
    - Current HRPO-approved consent form(s) (PDF)
    - Publications/abstracts/posters (PDF)
    - DSMB outcomes letter, if applicable (PDF)
- Blinded studies: Send the final DSM report to the statistician so they can prepare their report to send directly to QASMC.
- Pre-review of DSM report: Be sure to review and address each point from the pre-review email and reply to the pre-review email with all required updates/documents by the due date noted in the pre-review email.