

Yale Cancer Center Protocol Review and Monitoring System Accrual Monitoring Policy

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1.0 INTRODUCTION

1.1 Background

The National Cancer Institute (NCI) Cancer Center Support Grant (CCSG) guidelines call for a mechanism for assuring adequate internal oversight of the scientific aspects of all the cancer clinical trials in the institution. The focus of the Protocol Review and Monitoring System (PRMS) is scientific merit, prioritization, and progress of cancer clinical trials. The PRMS has the authority to open protocols that meet the scientific merit and scientific priorities of the center and to close protocols that do not demonstrate scientific progress. The Protocol Review Committee (PRC), Yale Cancer Center's (YCC) PRMS, is responsible for monitoring the accrual and scientific progress of all active, interventional, cancer and cancer-related clinical trials. This is facilitated through an annual review of scientific progress and a report of accrual for all open to accrual cancer and cancer-related clinical trials.

1.2 Definitions

Clinical Trials Advisory Committee (CTAC): An oversight body of the YCC comprised of senior leadership from the YCC and Smilow Cancer Hospital

Office of Quality Assurance and Monitoring: Office within the Yale Center for Clinical Investigator (YCCI) who is responsible for providing administrative support to the YCC review committees

OnCore: Yale University School of Medicine's Clinical Trials Management System

Trials of Rare Diseases: Per the NCI, incidence rate of \leq six newly diagnosed persons out of a population of 100,000 persons per year (\leq 6/100,000 per year)

IRIS IRB: Yale University's electronic submission and review system for human subjects' research studies

2.0 ACCRUAL MONITORING POLICY

2.1 Accrual Monitoring Rules for Non-Rare Trials

The following accrual monitoring rules will be applied for all interventional cancer and cancer-related clinical trials that are open to enrollment, except for trials of rare diseases or rare molecular sub-types. Trials with dose escalation and dose expansion phases will be evaluated according to the criteria provided below and will follow the *Protocol Review Committee OnCore Instructions for Dose Escalation/ Dose Expansion Studies* for dose escalation accrual targets to be accurately monitored.

2.1.1 Accrual Monitoring Table

Assessment Time	Percentage of Target Accrual Rate	Action
3 months	0%	Notice
6 months	0%	Warning
9 months	0%	Closure Recommendation
9 months	< 30%	Warning
12 months	< 30%	Closure Recommendation
15 months	< 40%	Warning
18 months	< 40%	Closure Recommendation
21 months	< 50%	Warning
24 months	< 50%	Closure Recommendation

After 24 months open, trials continue to be evaluated for accrual rate and will receive warning letters at 27 and 33 months and closure recommendations at 30 and 36 months if not meeting $\geq 50\%$ of target accrual. Studies open to accrual longer than 36 months will continue to be evaluated for accrual rate every six months. Those studies not meeting $\geq 75\%$ of target accrual after 36 months will receive warning letters and may receive a closure recommendation at the discretion of the PRMS.

2.1.2 Calculation of Percentage of Target Accrual Rate

$$\frac{\text{Actual Accrual}}{\text{Current \# of days open}} \div \frac{\text{Target Accrual Goal}}{\text{Expected Duration (days)}}$$

Example: A trial has an expected accrual duration of 365 days with an expected accrual of *eight* study participants. At the time of review, the trial has been open 377 days with *two* accruals to date. Since the trial has been open for more than 12 months with only 24% of the target accrual rate reached, the trial will be issued a closure notice.

$$\frac{2}{377} \div \frac{8}{365} = .2420 \text{ or } 24\%$$

2.1.3 Trials Meeting Target Accrual Rate, but with Zero Accrual in the Past Six Months

PRC will review interventional trials with zero accrual in the past six months. A response will be requested from the Principal Investigator (PI) regarding accrual plans and continued interest in enrolling to the trial. PRC may recommend closure of these trials.

2.2 Guidance for Trials of Rare Diseases and Rare Molecular Subtypes

The PRC will review accrual targets and screening efforts for trials of rare diseases and rare molecular subtypes during scientific progress reviews. Refer to Yale Cancer Center's Scientific Progress Policy for more information.

2.3 Accrual Monitoring Procedures

2.3.1 Identifying Trials of Rare Diseases and Rare Molecular Subtypes

The PI and research team will be responsible for identifying trials of rare diseases including rare molecular subtypes and uncommon clinical subsets of more common cancers on the *DART Protocol Review Form* (PRC submission requirement). The rare determination will be verified during PRC review. After verification at PRC review, the rare categorization will be captured in the risk assessment found in Yale School of Medicine's Clinical Trials Management System, OnCore, by Office of Quality Assurance and Monitoring Research Oversight Committee staff.

2.3.2 Principal Investigator's Role in Maintaining OnCore Study Record

The PI and research team are expected to maintain the study record in OnCore including any change in accrual goals as reported to the IRB of record (if required), change in anticipated primary completion date as reported in clinicaltrials.gov record, and updating the status to "suspended" during any periods when the study temporarily cannot enroll new participants (i.e., if the study is placed on hold by sponsor due to drug shortages, statistical analysis, etc.), in order to accurately assess accrual progress. The PI and research team are also responsible for updating the Rare Disease field in the main tab of the PC console of OnCore. Refer the [Guidance Document](#) for *OnCore New Study Data Entry Requirements* for more information.

2.4 Accrual Monitoring Process

The Yale Center for Clinical Investigation's (YCCI) Office of Quality Assurance and Monitoring is responsible for generating an accrual monitoring report from OnCore for PRC review approximately monthly. Notices, warning letters and closure recommendations are issued as the criteria in Section 2.1.1 are met. The Office of Quality Assurance and Monitoring Research Oversight Committee staff will be responsible for issuing the "Notice of No Accrual", "Accrual Monitoring Warning" and "Closure Recommendation Notice" on behalf of the PRC. The correspondence will be addressed to the PI with copy to the DART Leader and DART-specific Assistant Director for Clinical Trials Operations and Clinical Trial Team Manager (CTTM). A listing of notices, warning letters and closure recommendations distributed will be provided to the PRC at convened meetings via inclusion on the agenda.

Trials that meet the criteria for closure recommendation as outlined in Section 2.1.1, will receive a written letter to inform the PI and DART Leader that the study is scheduled for PRC review due to insufficient accrual and may be permanently closed to further accrual by the PRC. The *Accrual Monitoring Form* (Appendix 1) will be provided to the PI and DART Leader for review and completion prior to the scheduled PRC review date. Section I: Accrual Monitoring Report of the *Accrual Monitoring Form* is pre-populated by the Office of Quality Assurance and Monitoring Research Oversight Committee staff via report from OnCore. Section II: Principal Investigator Assessment and Justification of the *Accrual Monitoring Form* is completed by the PI and/ or DART Leader.

The closure review will be added to a PRC meeting agenda for discussion. The PI and/ or DART Leader will have the opportunity to provide justification to PRC for keeping a trial open to accrual despite low or no accrual via *Accrual Monitoring Form*. The *Accrual Monitoring Form* is submitted via ePRMS in OnCore.

The closure review will be assigned to one scientific reviewer. PI and/ or DART Leader justification will be reviewed along with a history of accrual monitoring, accrual progress and study status changes for the study lifecycle. The scientific reviewer will document their recommended decision on the *Accrual Monitoring Form*. The scientific reviewer may contact the PI and/ or DART Leader prior to the convened meeting to address any concerns or questions and will present the information to the PRC at the convened meeting and inform the committee of their recommended decision.

The PRC will discuss and vote to close or not close a study. For studies that are not closed, the PRC will require re-review within three months or six months. If, after the three- or six-month extension, the study does not meet the criteria met in 2.1.1, no re-review will be required. All other studies will be re-reviewed at a convened PRC meeting by the original reviewing PRC. Accrual progress during the extension will be provided to the committee for consideration. The PRC will vote to close or not close the study. The discussion and decision will be recorded

in the PRC meeting minutes.

The Office of Quality Assurance and Monitoring Research Oversight Committee staff are responsible for issuing a letter to the PI and DART Leader which states the decision made by the PRC during initial review and for any subsequent reviews including re-reviews.

Trials of rare diseases and rare molecular subtypes are not subject to accrual monitoring.

2.5 Closure of a Clinical Trial

Research Oversight Committee staff are responsible for changing the study status in OnCore to Closed to Accrual when the PRC decides to permanently close a study to further accrual following the convened meeting. The PI and research team are responsible for notifying the study sponsor of the PRC decision. The PI or their designee is responsible for notifying the IRB of Record of the PRC decision according to the IRB's written policies and procedures.

If a trial has not accrued study participants and the study sponsor agrees, paperwork may be submitted for IRB study closure and the OnCore status will be updated to IRB Closure accordingly. If a trial has participants on treatment or in follow-up, the trial will be closed to further enrollment. Permanent closure with the IRB will follow the policies and procedures of the Clinical Trials Office or department responsible for conduct of the study.

The PI and research team will take all necessary actions to comply with closure notices within 10 business days of receipt of the closure notice.

Appendix 1: Accrual Monitoring Form

Instructions: Review Section I: Accrual Monitoring Report and accompanying Closure Recommendation Notice for the study referenced below which is under consideration for closure by the Yale Cancer Center (YCC) Protocol Review Committee (PRC) due to low or no accrual. Complete Section II: Principal Investigator Assessment and Justification then submit form to PRC via ePRMS in OnCore by the deadline noted in the Closure Recommendation Notice.

Section I: Accrual Monitoring Report

Date of Accrual Monitoring Report:

HIC #

Principal Investigator:

Study
Title:

Yale Open to Enrollment Date:

Actual Months Open to Accrual:

Percentage of Target Accrual Rate:

See Figure 1.0 for the percentage of target accrual rate formula and Figure 2.0 for the Accrual Monitoring assessment schedule.

Accrual Monitoring History:

Section II: Principal Investigator Assessment and Justification

1. Overall Assessment:

- Agree with recommendation to close the study to accrual permanently.
- Disagree with recommendation to close the study to accrual permanently. Please answer questions below.

2. Why should the study remain open to accrual?

3. What strategies will be used to increase accrual in the next three (3) months?

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4. Are there competing protocols? (If yes, complete the table below for all competing protocols.)

Yes

No

HIC #	Short Title	Date Open to Accrual	Accrual Goal	# Enrolled to Date	Expected Closure Date	Comments on how priority will be assigned

FOR OFFICE USE ONLY:

PRC Reviewer's Name:

Principal Investigator did not provide a response.

Recommended Decision:

Recommend closure

Do not recommend closure

Re-evaluate in three (3) months

Re-evaluate in six (6) months

Provide explanation:

Additional Comments (optional):

Addendum 1: Re-review Following Extension

FOR OFFICE USE ONLY:

Date of Re-Review:

Duration of Extension:

Accrual during Extension:

Percentage of Target Accrual Rate:

Recommended Decision:

- Recommend closure
- Do not recommend closure

Provide explanation:

Figure 1.0 Percentage of Target Accrual Rate Calculation

Calculation of Percentage of Target Accrual Rate:

$$\frac{\text{Actual Accrual}}{\text{Current \# of days open}} \div \frac{\text{Target Accrual Goal}}{\text{Expected Duration (days)}}$$

Example: A trial has an expected accrual duration of 365 days with an expected accrual of 8 study participants. At the time of review, the trial has been open 377 days with 2 accruals to date. Since the trial has been open for more than 12 months with only 24% of the target accrual rate reached, the trial will be issued a closure notice.

$$\frac{2}{377} \div \frac{8}{365} = .2420 \text{ or } 24\%$$

Figure 2.0 Accrual Monitoring Assessment Schedule from Accrual Monitoring Policy

Assessment Time	Percentage of Target Accrual Rate	Action
3 months	0%	Notice
6 months	0%	Warning
9 months	0%	Closure Recommendation
9 months	< 30%	Warning
12 months	< 30%	Closure Recommendation
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Appendix 2 : Protocol Review Committee OnCore Instructions Dose Escalation/ Dose Expansion Studies

**Protocol Review Committee
OnCore Instructions
Dose Escalation/ Dose Expansion Studies**

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Determining Accrual Targets

Accrual targets are determined for studies at the time of Disease Aligned Research Team (DART) Protocol Review. The accrual information is noted in the Details Section of the Main Tab in the protocol record within the Clinical Trials Management System, OnCore and in the DART Protocol Review Form.

OnCore:

Accrual Information			Not Applicable <input type="checkbox"/>
Protocol Target Accrual*	<input type="text"/>	RC Total Accrual Goal (Lower)	<input type="text"/>
RC Annual Accrual Goal	<input type="text"/>	Affiliate Accrual Goal	<input type="text"/>
		RC Total Accrual Goal (Upper)*	<input type="text"/>
		Accrual Duration (Months)*	<input type="text"/>

DART Protocol Review Form:

If the study includes multiple phases, indicate how many subjects you expect to enroll in each phase.

Multi-phase Studies

Multi-phase studies that include dose escalation and dose expansion will be recorded as multi-phase studies in the Details Section of the Main Tab of OnCore. If the study includes multiple phases, the team will indicate in which phase they will participate on the DART Protocol Review Form.

OnCore:

Phase	<input type="text" value="v"/>
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Pick the appropriate Phase from the drop-down list. Typical options include IB/II or I-II.

DART Protocol Review Form:

If the study includes multiple phases, indicate which phase(s) Yale will be participating in.

Accrual Target

The accrual target for each phase will be noted in OnCore and within the DART Protocol Review Form for multi-phase studies that include dose escalation and dose expansion. The RC

[Research Center] Total Accrual Goal (Lower) will be used to note the Dose Escalation accrual target. After dose escalation is complete, the RC Total Accrual Goal (Lower) may be changed for accrual monitoring purposes by the study team. If the dose escalation and dose expansion target enrollment changes during the conduct of the study, the study team will update the targets in OnCore following IRB of record approval (if required). The dose escalation and dose expansion accrual targets will be noted in the DART Protocol Review Form.

OnCore:

Accrual Information				Not Applicable <input type="checkbox"/>	
Protocol Target Accrual*	<input type="text"/>	RC Total Accrual Goal (Lower)	<input type="text"/>	RC Total Accrual Goal (Upper)*	<input type="text"/>
RC Annual Accrual Goal	<input type="text"/>	Affiliate Accrual Goal	<input type="text"/>	Accrual Duration (Months)*	<input type="text"/>

DART Protocol Review Form:

If the study includes multiple phases, indicate how many subjects you expect to enroll in each phase.

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Suspending Arms/ Phases in OnCore

The Phases are noted in the Details Section of the Treatment tab in OnCore. The study team will ensure all relevant phases are noted at the time of OnCore Calendar Review before the study initially opens to accrual and when revisions are made due to an amendment.

Individual phases and arms will be suspended by the study team in the Details Section of the Treatment tab rather than at the Study Status level during dose escalation as enrollment is temporarily held by the sponsor. To avoid non-compliance, it is recommended that consent document(s) and study conduct document(s) that relate to suspended portion(s) of the study be temporarily removed from the Attachments Section of the Documents/ Info tab in OnCore. The phase/ arm suspension will be lifted when the sponsor allows enrollment to resume and the study team will update OnCore accordingly.

When a phase permanently closes to further accrual, i.e., the dose escalation period ends, the dose escalation phase(s) will be suspended in the Details Section of the Treatment tab. Consent document(s) and study conduct document(s) that relate to the permanently closed portion(s) of the study should be removed from the Attachments Section of the Documents/ Info tab in OnCore.

Select Protocol Type here to search	Details	Disease/Diagnosis
Main	Step 1 - Randomization	
Treatment	Arms	
Institution	Ph1b Sch1	Phase 1b: Trametinib Days 1-14 and Ribociclib Days 8-21 administered once daily of a 21-day cycle
Accrual		Suspended: No
Status	Drugs	
Reviews	Trametinib	
Documents/Info	Ribociclib	
Risk Assessment	Ph1b Sch2	Phase 1b: Trametinib and Ribociclib administered once daily on Days 1-14 of a 21-day cycle
Eligibility		Suspended: No
Protocol Calendar	Drugs	
Notifications	Trametinib	
	Ribociclib	
	Ph2 Sched1	Phase 2: Trametinib Days 1-14 and Ribociclib Days 8-21 administered once daily of a 21-day cycle
		Suspended: No
	Drugs	
	Trametinib	
	Ribociclib	

Study-wide Suspensions in OnCore

If at any time, enrollment to all enrolling parts of a study are suspended for any reason, the Status Section of the Status tab in OnCore will be updated to reflect a status of suspended for the study overall. Comments may be added to provide a rationale for the suspension.

Select Protocol Type here to search	Status	Task Lists
Main	Protocol Status	
Treatment	History	
Institution	Status Date	Status
Accrual	04/10/2018	SUSPENDED
	07/06/2017	OPEN TO ACCRUAL
	07/06/2017	PROJECT MANAGER SIGNOFF
	Initiator	Industry Sponsor
	Change Reason	Other
	Comments	Awaiting new amendment and Phase II dosing decision
	Last Changed By	[REDACTED]

Accrual Monitoring by Protocol Review Committee

The Protocol Review Committee (PRC) will consider accrual rates during dose escalation compared to dose expansion. It is expected that accrual will progress more slowly during dose escalation. For these considerations to be made by the PRC, the study team must adhere to the requirements listed above. The PRC will apply the *Accrual Monitoring Policy* to all open to accrual, non-rare, interventional cancer and cancer-related studies.