Yale Cancer Center
Accrual Monitoring Policy
Contents

1.0 INTRODUCTION ............................................................................................................................................. 3
  1.1 Background .................................................................................................................................................. 3
  1.2 Definitions .................................................................................................................................................. 3

2.0 ACCRUAL MONITORING POLICY .................................................................................................................. 3
  2.1 Accrual Monitoring Rules for Non-Rare Trials ............................................................................................. 3
    2.1.1 Accrual Monitoring Table .................................................................................................................. 3
    2.1.2 Calculation of Percentage of Target Accrual Rate ............................................................................. 4
    2.1.3 Trials That Have Not Reached Accrual Goal Prior to Anticipated Primary Completion Date .......... 5
    2.1.4 Trials Meeting Target Accrual Rate, but with Zero Accrual in the Past Six Months ....................... 5
  2.2 Guidance for Trials of Rare Diseases and Rare Molecular Subtypes ......................................................... 5
  2.3 Accrual Monitoring Procedures .................................................................................................................. 5
    2.3.1 Identifying Trials of Rare Diseases and Rare Molecular Subtypes .................................................... 5
    2.3.2 Principal Investigator’s Role in Maintaining OnCore Study Record ................................................ 5
  2.4 Accrual Monitoring Process ......................................................................................................................... 6
    2.4.1 Reassessment of Closure Recommendation ..................................................................................... 6
    2.4.2 PRC Ratification of PLCS Closure Recommendations ...................................................................... 6
  2.5 Closure of a Clinical Trial ............................................................................................................................ 7
  2.6 Appeal Process ............................................................................................................................................. 7
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 Life Cycle Subcommittee (PLCS) of the Protocol Review Committee (PRC), a component of Yale Cancer Center’s PRMS, is responsible for monitoring the accrual and scientific progress of all active, interventional, cancer clinical trials. This is facilitated through review of scientific progress and a report of accrual for all open to accrual cancer clinical trials.

1.2 Definitions
Clinical Research Oversight Committee (CROC): An oversight body of the Yale Cancer Center comprised of senior leadership from the Yale Cancer Center and Smilow Cancer Hospital.

Office of Quality Assurance and Monitoring: Office responsible for providing administrative support to the Yale Cancer Center review committees.

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

Trials of Rare Diseases: Per the NCI, incidence rate of ≤ 6 newly diagnosed persons out of a population of 100,000 persons per year (≤ 6/100,000 per year). Using definition or cut-off, virtually all pediatric cancer types would be considered “rare cancers.”

IRES 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
2.1.1 Accrual Monitoring Table
The following accrual monitoring rules will be applied for all interventional cancer 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 Life Cycle Subcommittee OnCore Instructions for Dose Escalation/ Dose Expansion Studies for dose escalation accrual targets to be accurately monitored.
<table>
<thead>
<tr>
<th>Assessment Time</th>
<th>Percentage of Target Accrual Rate</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>0%</td>
<td>Notice</td>
</tr>
<tr>
<td>6 months</td>
<td>0%</td>
<td>Warning</td>
</tr>
<tr>
<td>9 months</td>
<td>0%</td>
<td>Closure Recommendation</td>
</tr>
<tr>
<td>9 months</td>
<td>&lt; 30%</td>
<td>Warning</td>
</tr>
<tr>
<td>12 months</td>
<td>&lt; 30%</td>
<td>Closure Recommendation</td>
</tr>
<tr>
<td>15 months</td>
<td>&lt; 40%</td>
<td>Warning</td>
</tr>
<tr>
<td>18 months</td>
<td>&lt; 40%</td>
<td>Closure Recommendation</td>
</tr>
<tr>
<td>21 months</td>
<td>&lt; 50%</td>
<td>Warning</td>
</tr>
<tr>
<td>24 months</td>
<td>&lt; 50%</td>
<td>Closure Recommendation</td>
</tr>
</tbody>
</table>

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 ≥ 50% of target accrual. Studies open to accrual longer than 36 months will continue to be evaluated for accrual rate. Those studies not meeting ≥ 75% of target accrual 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

\[
\text{Actual Accrual} \div \text{Current # of days open} \div \text{Expected Duration (days)} = \text{Target Accrual Goal}
\]

**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.

\[
\frac{2}{377} \div 8 = 0.2420 \text{ or } 24\%
\]
2.1.3 Trials That Have Not Reached Accrual Goal Prior to Anticipated Primary Completion Date

Applicable to all interventional trials unless they are national or international cooperative group or industry studies which have not reached their overall accrual goals.

On the anticipated primary completion date, if trial has not reached total accrual goal, a warning notice is issued.

Six (6) months past the anticipated primary completion date, if trial has not reached total accrual goal, a recommendation for closure is provided by the PLCS to the PRC.

The PRC will vote on and ratify all PLCS closure recommendations. The PLCS will also receive a report of PRC accrual monitoring decisions.

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

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

The PRC will vote on and ratify all PLCS closure recommendations. The PLCS will also receive a report of PRC accrual monitoring decisions.

2.2 Guidance for Trials of Rare Diseases and Rare Molecular Subtypes

The PLCS 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. The PLCS will review screening activity for the prior scientific review period (approximately 12 months) for consideration.

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 discussed and verified during PRC review. After verification at PRC review, the rare categorization will be captured in Yale School of Medicine’s Clinical Trials Management System, OnCore.

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, change in anticipated primary completion date, and updating the status to “suspended” during any periods when the study temporarily cannot enroll new participants (for example if the study is placed on hold by sponsor due to drug shortages, statistical analysis, etc.), in order to accurately assess accrual.
2.4 Accrual Monitoring Process

The Office of Quality Assurance and Monitoring will be responsible for generating an accrual monitoring report from OnCore for PLCS review. Notices and warning letters are issued as the criteria in Section 2.1.1 are met. A report of notices and warning letters distributed will be provided to the PLCS at convened meetings. Those trials that meet the criteria for closure recommendation, as outlined in Section 2.1.1, will be added to the PLCS meeting agenda for discussion. Trials of rare diseases and rare molecular subtypes will not be included in the discussion.

The PLCS will discuss and decide if a trial will be recommended for closure to the PRC. If consensus is reached by the PLCS, the PI will be notified and the trial will be scheduled for discussion at an upcoming PRC meeting.

The Office of Quality Assurance and Monitoring will be responsible for issuing the “Notice of No Accrual”, “Accrual Monitoring Warning” and “Closure Recommendation Notice” on behalf of the PLCS. The correspondence will be addressed to the PI with copy to the DART Leader, Assistant Director of Clinical Trials Operations in Clinical Research, Assistant Director of Clinical Trials Operations in Regulatory Affairs, Clinical Trial Team Manager (CTTM), and Regulatory Assistant.

2.4.1 Reassessment of Closure Recommendation

Upon receipt of a “Closure Recommendation Notice” from the PLCS, if the PI would like to have the closure recommendation reassessed by the PLCS, the Office of Quality Assurance and Monitoring must be notified by the PI in writing within 10 business days. The PI will need to explain barriers to enrollments, provide a plan for increasing accrual and a justification for keeping the trial open.

If a request to reassess a closure recommendation is received within 10 business days and time permitting, the PLCS Chair may review the request to determine if the PI needs to attend the PRC meeting, either in person or remotely, to discuss the trial or if the PRC’s review of the PI’s request to reassess is sufficient.

2.4.2 PRC Ratification of PLCS Closure Recommendations

The PRC will vote on and ratify all PLCS closure recommendations. The PLCS will also receive a report of PRC accrual monitoring decisions.

The Office of Quality Assurance and Monitoring will be responsible for issuing the accrual monitoring decision letters on behalf of the PRC. The correspondence will be addressed to the PI with copy to the DART Leader, Assistant Director of Clinical Trials Operations in Clinical Research, Assistant Director in Clinical Trials Operations in Regulatory Affairs, CTTM, and...
2.5 Closure of a Clinical Trial
The PI and research team are responsible for updating the OnCore status as well as submitting
the necessary paperwork to the study sponsor and the IRB of Record according to their policies
and procedures. The Office of Quality Assurance and Monitoring will monitor the status in
OnCore to ensure that the status of the trial is updated accordingly. If a trial has not accrued
study participants and the study sponsor agrees, paperwork will be submitted for IRB study
closure and the OnCore status will be updated accordingly. If a trial has participants on
treatment or in follow-up, the trial will be closed to further enrollment. The Office of Quality
Assurance and Monitoring will monitor the status in OnCore until the trial is permanently
closed with the IRB of record.

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.

2.6 Appeal Process
The PI may request reassessment of the PLCS closure recommendations within 10 business
days, as outlined in 2.3.4 above, and request appeal of PRC closure decisions to the PRC within
10 business days. The PI will explain barriers to enrollments, provide a plan for increasing
accrual and a justification for keeping the trial open.

Reassessment and appeal requests regarding decisions from PLCS and PRC may be submitted to
the Clinical Research Oversight Committee (CROC) for review and discussion.

During the appeal process, no new study participants may be accrued. The study status will be
changed to “Suspended” in OnCore.

The CROC review and recommendation on the appeal will be submitted to the PRC for their
decision on the appeal.

The PRC has final and absolute authority on all appeals related to the PRMS. The PRC has the
authority to close any study.