

Continuing Review: It Doesn't Have to be an Excruciating Process!

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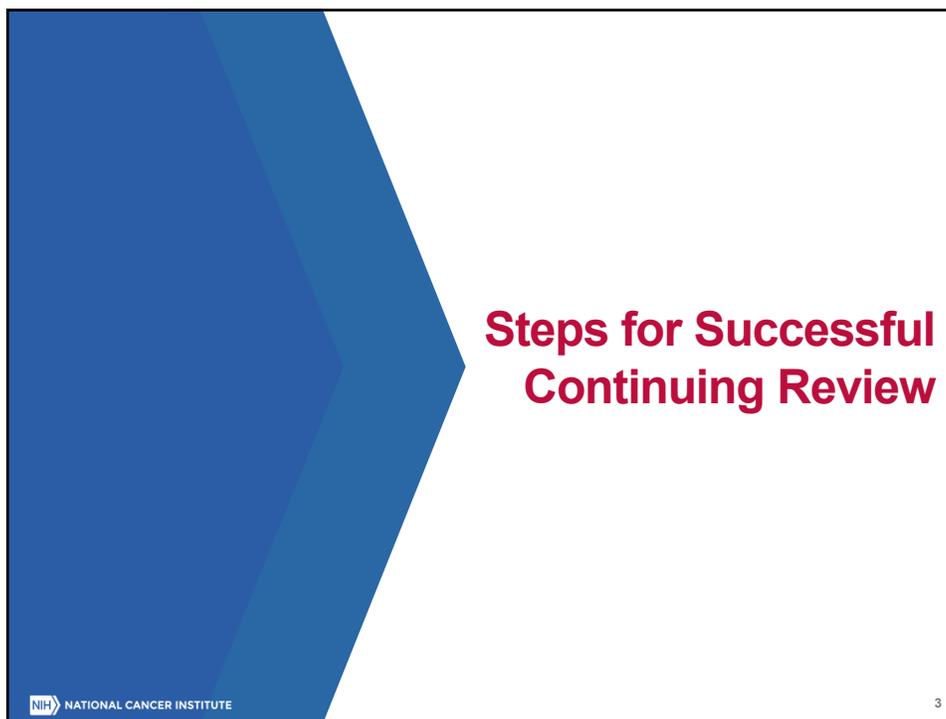


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Continuing Review

- Continuing reviews are conducted to assure the protection of the rights and welfare of human subjects participating in research.
- Revised Common Rule: Research approved by the IRB on or after January 21, 2019, continuing review may no longer be required for certain categories of minimal risk research.

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Step 1: Know Your Due Date

- **Frequency of Continuing Review**
 - The IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less often than once a year (45 CFR 46.109(e)).
 - The IRB may decide more frequent reviews are appropriate. For example, when the risks to subjects warrants more frequent reassessment, the IRB should specify the duration of the approval period and the interval by which continuing review must occur (e.g., 4 months, 6 months, or 1 year).

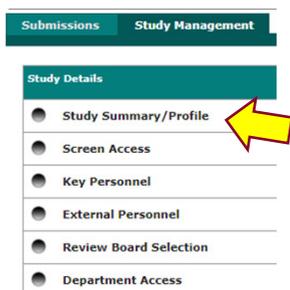
 *Hint: if no expiration date is listed, the protocol may fall under the new revised common rule that Minimal Risk studies no longer require continuing review. However, the NIH IRBO may require a progress report.*

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Step 1A: Locate expiration date

- In iRIS, go to: Study Management, then Study Summary/Profile



NIH IRB	
IRB Number:	09C0100
IRB of Record:	Yes
Committee of Record:	Panel 1
IRB Initial Approval:	12/15/2008
Review Cycle:	12 Months
IRB Expiration Date:	10/05/2021
Last Continuing Review Approved:	10/06/2020
Continuing Review Due:	08/05/2021

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Step 2: CR Notification

- The NIH IRB requires the continuing review to be submitted 6 weeks prior to the expiration date.
- iRIS will *generally* email 3 automatic Continuing Review notifications:
 - ~60 days prior to the expiration date
 - ~30 days prior to the expiration date
 - ~6 weeks prior to the expiration date → "Now Due"
- Your PSO Manager will contact you approximately 10 weeks prior to the protocol expiration date. In that contact will be the request for information to include/gather for the CR submission.

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Step 3: Gather Information Needed for CR...

- According to 45 CFR 46.103(b)(4), the investigator is responsible for submitting sufficient materials and information for the IRB to meet its regulatory obligations and follow the institutional policies and procedures for continuing IRB review of research.
- Some information or data to consider:
 - What is the protocol progress or findings from your research?
 - Have you met your primary outcome?
 - How many deviations, non-compliance, or UPs have occurred since the last review? If there were any, how has it impacted your research?
 - Are your adverse events or SAEs within the expected severity and frequency? Do the adverse events alter the level of risk of the study?

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...Step 3: Gather Information Needed for CR...

- Other information to consider or gather.
 - How many participants have you enrolled since the last review? What is the total number of participants enrolled on study.
 - Have any participants withdrawn from study? Are any participants lost to follow-up? Were there any screen failures?
 - Has the short form consent been used? If so, how many did you use and in what languages?
 - Was accrual lower than expected during the review period?



Hint: Always review the previous CR so the information is consistent with the current CR.

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...Step 3: Gather Information Needed for CR

- Redacted Consents
 - Have any subjects **enrolled** since the last review?
 - If yes, you will need to forward a scanned redacted copy of the last signed consent for each of the approved forms used during the review period.
 - Participant identifiers, such as name and medical number, including the barcode **MUST** be blacked out. Also, the participant's signature needs to be entirely blacked out.
 - **DO NOT** black out "the date" the participant signed consent, or the signature of the investigator and the date consent was signed.

Step 3A: Redact Consent



Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and ask questions. I consent to participate in this study.

Signature of Research Participant _____ First Name of Research Participant _____ Date 11/23/2020

Investigator:
Signature of Investigator [Signature] First Name of Investigator Anna Conville Date 9/23/2020

Witness to the oral short-form consent process only: This section is only required if you are doing the oral short-form consent process and this English consent form has been approved by the IRB for use as the basis of translation.

Witness:
Signature of Witness* N/A First Name of Witness N/A Date _____

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____

FATIENT IDENTIFICATION Consent to Participate in a Clinical Research Study
NCR 2017 (v-12)
File in Section 6 Protocol Consent (1)
Version Date: 05/26/2020
Page 11 of 11
IRB NUMBER: 19C0040
IRB APPROVAL DATE: 03/28/2020

Step 4: Progress Report

- For research approved by an IRB on or after January 21, 2019, continuing review will no longer be required for certain categories of minimal risk research, unless specifically required by the IRB.
- The IRB may still require a “check in”. It’s a simple form with five questions:
 - Accrual Status
 - Study Completion Date
 - Primary Completion Date
 - Study Population
 - Enrollment Table



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What are the timelines?

Important Dates	Timing Prior to Protocol Expiration
Continuing Review Due	~ 6 weeks prior
IRBO 1 st Notification*	~60 days prior
Continuing Review Data Cut-Off	~75 days prior
Response from Study Team Due	~7 weeks prior



You will receive PSO’s request for information approximately 10 weeks prior to protocol expiration date.

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Questions

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Review of Sections: Continuing Review Information Request

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Accrual/ Recruitment Status

- Update overall status
- If recruitment slower than expected, indicate plan to increase recruitment and impact on objectives and scientific integrity
 - Refer to statistical section in protocol for annual accrual rate

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Completion Dates

- Study Completion Date – update as needed
 - The date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events
- Primary Completion Date – update as needed
 - The date that the final subject will be examined or an intervention received for the purposes of final collection of data for the primary outcome

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Protocol Progress / Findings

- Should be completed by PI and/or lead AI
- Summarize protocol progress to date and any results
 - How many enrolled and how many have completed treatment?
 - Any arms/cohorts are completed?
 - What was response of patients that completed treatment?
 - How many DLTs?
- Do not include a summary of each patient

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Protocol Progress Example . . .

A total of 23 patients have enrolled since the initiation of the study with 6 patients accrued since the last CR. Both Arm A (M7824 monotherapy) and Arm C (M7824 plus temozolomide) have completed enrollment for the SCLC cohort. There is an additional cohort of up to 10 patients with extrapulmonary small cell cancer to be enrolled in Arm C. Primary and secondary objectives of Arm B (topotecan plus M7824) and the exploratory extrapulmonary small cell cancer cohort have not been met and the protocol is enrolling as planned. There has been a total of 10 deaths from progressive disease (PD) since last CR and a total of 19 PD deaths since the initiation of the study.

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Protocol Progress ... Example ...

Between date 7/1/19 and 4/15/2020, 10 patients (6 patients since last CR) enrolled on Arm C (M7824 with temozolomide). All 10 patients are off treatment at the time of this report. Eight patients came off treatment for PD (including 2 patients who had clinical progression), 2 patients came off treatment respectively for pandemic-related travel restrictions/risk and persistent toxicities. Of 10 evaluable patients on Arm C, one patient had partial response. He remained on treatment for 10 months before coming off treatment for pandemic-related travel restrictions/risk. He is currently on follow up without any additional treatments.

Protocol Progress ... Example

Since the last CR, one patient had three hospitalizations for ileus possibly related M7824. The patient came off treatment after approximately 7.5 months for persistent GI symptoms. The patient had stable disease throughout and died 2.5 months later. Another patient developed immune related rash C1D4 of Arm C. The patient completed >30 days of prednisone and was able to restart therapy. He was on trial for 4 months and came off for PD. He remains on follow up.

Reportable Events . . .

- Provide high-level summary of events since last CR
 - Major and minor deviations
 - Noncompliance that is not a deviation
 - Unanticipated problems
 - Serious adverse events that are not UPs
 - Adverse events
- Must include events already reported to IRB (major deviation, noncompliance, UP) and indicate REF number
 - Report in iRIS

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Reportable Events . . .

- Indicate if a review of reportable events impacts patient safety or scientific integrity of the study
- If AE information is included in protocol summary, make sure information is consistent in this section
- Make sure the numbers add up!!
- DO NOT submit a line-by-line listing of deviations or SAEs/AEs

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Reportable Events Report . . .

The screenshot shows a web application interface. At the top, there is a navigation bar with 'Help', 'Tutorial', 'My Profile', and 'Log out'. Below this, a 'Tasks' section is visible. A dropdown menu is open, showing categories: 'SETTINGS', 'RESOURCES', 'COMMUNICATIONS', 'REPORTS & CONFIGURATION', and 'MISCELLANEOUS'. Under 'REPORTS & CONFIGURATION', 'My Reports' is highlighted. A red arrow points to the 'My Profile' dropdown, and another red arrow points to the 'My Reports' item.

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. . . Reportable Events Report . . .

The screenshot shows a list of reportable events. The list is organized into sections: 'PRO', 'PSO', 'Review Board', and 'SMC'. Under 'PRO', there are items like 'Outstanding Internal Submission Routing (CSV)' and 'Short Consent Approval Form Report (CSV)'. Under 'PSO', there are items like 'Adverse Event Report (NIH Problem Form) - PDF' and 'Approved Amendment(s), CR(s) and Study Status Change(s) per Study - (CSV)'. Under 'Review Board', there is an item 'Expedited Actions Report - (PDF)'. Under 'SMC', there is an item 'SMC Review Protocols (CSV)'. A red arrow points to the 'Expedited Actions Report' item.

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... Reportable Events Report ...



iRIS by MedRIS
Integrated Research Information System

Account: Deborah Grady
Branch: NCI - C - Office of the Clinical Director
Path: Home > granted_reports_access

My Workspaces ▾ My Profile

List of Deviation(s), UP(s) and Non-compliance(s) per Protocol - (PDF)

Display Report as: PDF HTML Excel CSV

Please Enter the Protocol Number: 

Enter protocol number and click Run Report

Help My Profile ▾ Log out

Back

Helpful Information
Run Report 

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... Reportable Events Report

Deviation, Unanticipated Problem and Non-compliance Report

Protocol	PI	Ref #	Determination	IRB Determination	Date of Event	Date IRB Notified	Name the Event	Description	Corrective Action
01C0129	Guley, James	551556	Non-compliance: Other			11/05/2020	Informed consent issue	At the time the last amendment was approved (August 31, 2020), 58 people were enrolled on the protocol. The teams were notified that, per the IRB outcome letter, patients do not need to be re-consented but will need to be contacted and notified of the changes to the consent. The teams were given 2 weeks to notify the patients or take them off the protocol. An audit was conducted to determine if patients were notified of the changes. As of September 14, 24 patients had not been notified of the changes in the informed consent. Of those, 10 patients were subsequently notified of consent changes or taken off study. In addition during the audit it was found that 5 patients that signed the consent form did not have any documentation of the informed consent process in CRIS; therefore there is no documentation that a copy of the consent document was given to the patient as required by the Common Rule.	No action required
01C0129	Guley, James	549932	Non-compliance: Other	Non-compliance: Not serious or continuing	05/11/2020	09/30/2020	Informed consent issue	During an internal informed consent audit, three issues were found that require reporting to the IRB. Issues 1 and 2 occurred with the same patient. Issue 3 occurred with a different patient on a different team. 1. An investigator obtained informed consent but was not listed on the protocol's Key Study Personnel form at the time of consent. 2. A Portuguese-speaking patient was enrolled using the short form process, an interpreter was utilized and a witness was present. However, the patient was incorrectly instructed to sign the English long form consent as well as the short form Portuguese consent. 3. A Spanish-speaking patient was consented	No action required

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Deviations Example . . .

There have been 39 minor protocol deviations since last CR: 26 were due to Covid19 restrictions of which 25 were related to research studies (research labs, PKs and hair follicles) not being collected due to lack of staffing and one related to delayed study visit (by a day); 13 were due to other minor deviations which included: 9 related to laboratory procedures (temozolomide PKs not collected due to collection time falling outside lab processing hours, C2 pre-dose research labs omitted on a patient for grade 3 anemia, and research tube damaged in transit), three related to non-lab study procedure/assessment (missed vital signs) and one SAE reporting which was late by a few days when patient was admitted for observation for Bactrim initiation.

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Deviations . . .Example

There were no reportable major deviations or noncompliance during this reporting period. The PI reviewed all deviations and determined that in aggregate, patient safety was not impacted nor was the scientific integrity of the study. All deviations were reported to the sponsor as required.

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Adverse Events Example . . .

There were a total of 10 SAEs: 1 patient died due to progressive disease within 30 days of treatment; 2 patients with dyspnea due to disease; 2 patients with lung infections - one unrelated to study drugs, one related to temozolomide only; 1 patient with superior vena cava syndrome related to disease; 3 hospitalizations from 1 patient for ileus possibly related M7824; 1 patient with hypoxia, sepsis, encephalopathy and lung infection unrelated to study drugs.

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Adverse Events . . . Example . . .

The following laboratory AEs were considered clinically significant: 7 blood and lymphatic system; 7 endocrine, metabolism and nutrition disorders. In addition, the following non-laboratory AEs occurred: 3 Cardiac disorders (tachycardia, pericardial effusion) , 3 Eye disorders (blurred vision and swelling), 24 Gastrointestinal disorders (nausea, vomiting, diarrhea, etc) , 23 Respiratory disorders (shortness of breath, low oxygen level, cough, sinus issues, etc), 3 infections (ear, UTI, herpes reactivation), 13 Musculoskeletal and connective tissue disorders, 15 Nervous and Psychiatric system disorders (headache, change of taste, etc) ; 6 Vascular disorders, 14 Skin and subcutaneous tissue disorders (rashes, etc); 14 General disorders (fatigue, fever, etc) and injuries (bruising and fall), 1 urinary incontinence, 1 pelvic pain.

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Adverse Events . . . Example

There were no unanticipated problems during the reporting period.

All adverse events were reviewed by the PI and are within the known risk profile for this study. We continue to monitor closely for immune related adverse effects to determine any increased risk for study patients.

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IRBO – Tips and Tricks

- Example high-level summary: *There were a total of 10 deviations that have occurred, which included 8 out of window visits due to inclement weather or scheduling issues with the participants, and 2 participants failed to bring their medication diary to a follow up visit. There were no systemic issues identified with these deviations.*

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IRBO – Tips and Tricks

- *Adverse events that have occurred over the past year are within expected severity and frequency and do not alter the level of risk of this study*
- OR
- *The frequency and severity of adverse events does not exceed what is described in the protocol and consent*

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Enrollment Table

Status	Number of subjects enrolled
Screen failures	
Currently undergoing study interventions and/or procedures	
Completed study procedures and now in follow-up	
Completed follow-up/off study	
Withdrawn from study, no further follow-up	
Lost to follow-up	
Deaths (related to research)	
Deaths (unrelated to research)	
Total number of subjects enrolled to date	

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Enrollment Table

- *Screening failure* – DO not include numbers from patients enrolled on screening protocol
 - If using screening protocol, will be “0” on this line
- *Completed study procedures and now in follow-up*: long-term survival follow-up
 - If patients are enrolled on a long-term follow-up study (e.g., s/p gene therapy), then considered “off study” for the treatment protocol
- *Withdrawn from study, no further follow-up*: refer to protocol for off-study categories (e.g., if patient noncompliance; study early stopping)
- Deaths while on study only

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Enrollment Table

- Make sure that numbers add up and are consistent with information from other sections (e.g., in protocol summary, if 10 patients off study, then there must be a “10” listed in the table for “Completed Follow-up/off study”)

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Literature Review / Publications

- PI should provide this information
- Summarize anything in the literature since the last CR that might impact risk/benefit of study
- List publication from the data from this study (manuscripts and abstracts)

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Justification for Continuation

- Example:

Primary and secondary objectives have not been met and the protocol is enrolling as planned.

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Summary

- Provide the PSO with your CR information no later than the due date in the email or EARLIER if possible
- Gather reports (CR AE report from DMs, REFs from iRIS, etc) prior to completing the CR request
- Do not send back CR request to PSO Manager until all sections / questions are answered
 - Rename file to distinguish different versions
- Please spell out all acronyms

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QUESTIONS



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