

ALL ABOUT CRS:

Tips for Making the Submission Process Easier

AGENDA: behind-the-scenes look at how the IRB evaluates CR submissions

Why CRs?

- Assessing that the study is meeting approval criteria
- Outline the review process for how that's assessed

Components of a CR

- What information is necessary for each aspect
- Examples of great submissions & examples of each

Bonus Tips

- Information only has to be listed in one location
- Site-specific information is always helpful overall

REMEMBERING THE **PURPOSE** OF
CONTINUING REVIEWS

WHY A CR? : Re-evaluate and confirm that the study still meets criteria for approval.

Risks to subjects
are reasonable

Selection of
subjects is
equitable

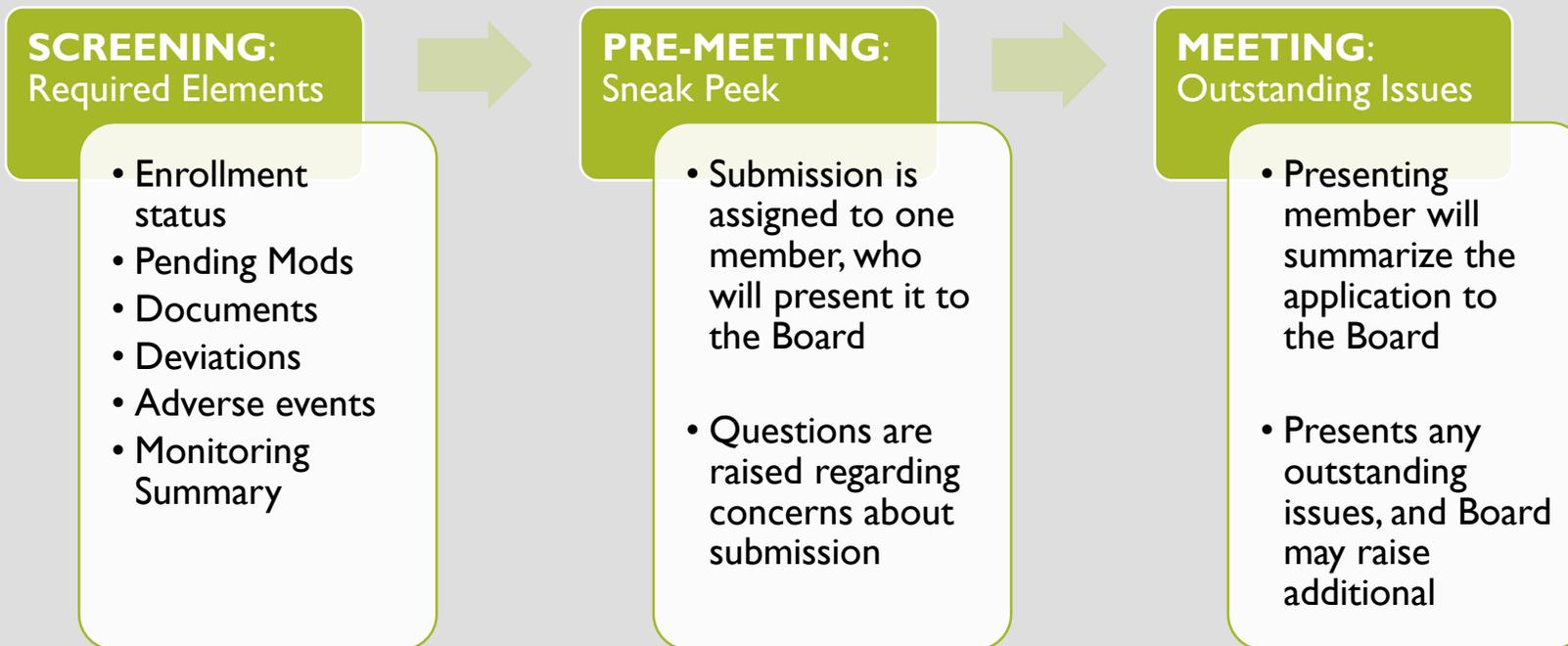
Informed consent
sought &
documented

Adequate
Monitoring

Adequate
Protection of
Privacy &
Confidentiality

All Added
Safeguards in
Place

CR REVIEW PROCESS: CR goes through three key stages to be approved.



**COMPONENTS OF A CONTINUING
REVIEW APPLICATION**

DOCUMENTS: Incorporate the documents necessary to see the study's current status.

A. Documents: *One Copy* of each of the following documents may be required for continuing approval (for both biomedical and social/behavioral research):

- Completed Continuing Review Form, (Paper submissions require PI signature)
- Progress Report (See Section B for details)
- The currently approved protocol document and protocol summary (if applicable)
- Currently approved versions of Informed Consent Forms (unless enrollment is permanently closed or no informed consent forms are required or used in the research)
- Applicable Supplemental Reports (See Section C for details)

For Biomedical Research Only:

- Currently approved Investigators Brochures and/or Package Inserts for all study drugs/devices

ENROLLMENT: Include consistent evaluation of status & withdraws in particular

How many enrolled in last review period

How many withdrew, and why

All numbers must be consistent throughout

ENROLLMENT: Need consistent evaluation of status & withdraws in particular

To the right is an example of an excellent enrollment summary from a CRU submitter.

Result: no further questions were

“The study opened to enrollment at Penn on 09/22/2015. Arm B part 2 (first line patients with pancreatic cancer) is the only cohort we have enrolled to this year. At this time all slots have been filled. Since the study opened a total of twelve patients have signed consent, six since the last continuing review. Of those only one was a screen fail; the patient decided not to go on study.

“There are two active patients at our site (0151007 and 0151011) and one in follow-up for survival (0151005). Since the last review, 5 patients came off study; three who did not want to continue treatment and one was the treating physician’s decision. The two active patients continue to be treated with Nivolumab on day 1 and 15 of a 21 day cycle and gemcitabine and nab-paclitaxil on days 1, 8, and 15 of a 21 day cycle.”

ADVERSE EVENTS: Need site-specific evaluation of how many and how they met (or did not meet) the reporting criteria

For Non-Reportable AEs: a table or narration are both acceptable formats

Date of Event	Event Description	Expected or Unexpected?	Related or Unrelated?	Are any revisions necessary?

For Progress Report: consider whether there were any patterns of minor deviations over the past year & if a plan is needed

ADVERSE EVENTS: Need site-specific evaluation of total and reporting criteria

To the right is an example of an exemplary adverse event summary from a CRU submitter.

Result: the reviewer really appreciated this summary and no added emails were sent regarding AEs or issues raised in the meeting.

“Since the time of the last continuing review, treatment has been generally well tolerated. The majority of adverse events have been mild to moderate and expected toxicity associated with one or both Chemotherapy Agents or that of metastatic Pancreatic Cancer Patients. The most common adverse events have been Gastrointestinal (nausea, vomiting, anorexia, and diarrhea); Fatigue, and myelosuppression. These adverse events have not been more frequent or severe in their occurrence. All AE/SAE information has been collected, documented, received, and reported in accordance with the protocol, as well as, local and institutional requirements

“Serious Adverse Events that have occurred since the time of the last continuing review are listed below.

2031-2158: Grade 2 Pleural Effusion, unrelated to study drugs, related to progressive disease

These serious adverse events did not meet the IRB reporting criteria as they were expected adverse events related to the chemotherapy agents or unlikely or unrelated to the clinical trial therapy.”

DEVIATIONS: Include summaries of the deviations and rationales for their assessments.

For Minor Deviations: consider a table (or narration) to cover all required elements

Date of Deviation	Description	Previously Reported to the IRB (Y/N)	Corrective Action Taken	Impact to Rights, Welfare, & Willingness?	Impact to Scientific Integrity?	Potential to Impact Safety of Subjects?

For Progress Report: consider whether there were any patterns of minor deviations over the past year & if a plan is needed

DEVIATIONS: Include summaries of the deviations & rationales for assessments.

To the right is an example of an strong deviation summary from a CRU submitter.

Result: the reviewer raised no further questions, and the study was placed for review and approved.

“There was one deviation that occurred on this study during the last approval year. For subject 840005203, on 10/25/17, week 5 day 2 CRP testing was not drawn. This was due to an error with nursing in the CHPs center. They used the CRP order for this date on 10/24/17 by accident. This did not compromise subject safety or data integrity.”

MONITORING: Outline study-specific plan of how monitoring plan is conducted

Clearly state the monitoring plan

Explicitly state whether there is a DSMB

Outline how the plan was/was not followed & why

Describe whether there were findings that impacted safety, rights, or integrity

If so, outline what those were and how they were handled

MONITORING: Outline study-specific plan of how monitoring plan is conducted

To the right is an example of a very strong monitoring summary from a CRU submitter.

Result: the reviewer had no further questions about the PPDI evaluation, and the study was approved.

“This study is monitored by PPDI. As of July 2017 the site monitor was changed. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject’s source documents, and all other study documentation are inspected/reviewed by the PPDI representative in accordance with the Study Monitoring Plan. They return every four weeks for monitoring.

“The follow up letters issued at the completion of monitoring visits were received, reviewed and filed as appropriate. No findings were suggestive of issues which could impact the rights and welfare of human subjects.”

PENDING MODS: Check and report if there are incoming modifications or deviations

Incoming Modifications

- If an incoming protocol amendment/IB is coming in, state what it is and its current status
- If an update to align with the latest IB is coming, state that

Present/Past Reviewed Submissions

- State if anything is currently under review (e.g. a deviation or a modification)
- Include any information about re-consenting still underway

BONUS TIPS FOR CONTINUING
REVIEW APPLICATIONS

CR TIP #1: Most important component of a review is that the **information is somewhere.**

CR Form: presentation
of some of the
necessary data
(e.g. enrollment stats, etc.)

Progress Report:
clarification of data +
added descriptions
(e.g. re-consent status, etc.)

CR TIP #2: This information must elucidate the specific study's status for the reviewer.

Reviewer assesses details of study's progress thus far to determine approval.



Providing those specific details upfront can often significantly shorten the review process.

YOU BE THE REVIEWER ROUND
FOR CONTINUING REVIEWS

“YOU BE THE REVIEWER” ROUND!

Evaluating CRs

Monitoring Summary: “The monitoring plan was followed as outlined in the protocol with no concerns raised.”

INCOMPLETE:

Need to outline what the monitoring plan is for this study, how it was followed, and what types of concerns were raised/not raised

“YOU BE THE REVIEWER” ROUND!

Evaluating CRs

Pending Modification: “We expect an incoming modification to submit a new Spanish consent form due to the number of Spanish-speaking subjects enrolled in the study. In addition we are currently awaiting convened review of _____ under IRB #2.”

COMPLETE:

Clearly outlined what other actions are in motion or will be in motion regarding the study itself

“YOU BE THE REVIEWER” ROUND!

Evaluating CRs

Date of Deviation	Description	Previously Reported to the IRB (Y/N)	Corrective Action Taken	Impact to Rights, Welfare, & Willingness?	Impact to Scientific Integrity?	Potential to Impact Safety of Subjects?
05/11/17	Out-of-window visit	N	None	N	N	

INCOMPLETE:
 Need to outline the details of each category & how that assessment was made; otherwise, the Board can't corroborate evaluation
Result: follow-up questions

“YOU BE THE REVIEWER” ROUND!

Evaluating CRs

Deviations: “There was one deviation reported in the last year but it was resolved appropriately.”

INCOMPLETE:

Need to outline what the deviation was, the date it occurred, the actions taken, and the three assessments

“YOU BE THE REVIEWER” ROUND!

Evaluating CRs

Date of Deviation	Description	Previously Reported to the IRB (Y/N)	Corrective Action Taken	Impact to Rights, Welfare, & Willingness?	Impact to Scientific Integrity?	Potential to Impact Safety of Subjects?
04/23/18	For Subject 10548, an MRI was accidentally not performed at Visit 48 due to subject request to not have it performed.	No: this is being reported at time of continuing review since it was evaluated by the study team to not meet the reporting criteria.	Since MRI is standard-of-care and a number of other procedures are in place to assess subject’s health status in follow-up, we determined no MRI was needed. We did note this for the upcoming visit to see if the subject is more amenable.	No: this deviation occurred in order to enhance & respect subject’s rights and welfare by not performing added procedure if not necessary and if they felt strongly against it.	No: the MRI is standard-of-care and does not impact the endpoints of the study.	No: the added tests performed as part of the study increased monitoring and allowed us to assess status in other ways

COMPLETE:
 Clear extent of the deviation, and clear assessments provided for reviewer’s evaluation

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