

Re-envisioning Memorial Sloan Kettering Cancer Center's Data and Safety Monitoring Committee

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Background

- Memorial Sloan Kettering Cancer Center's (MSK) Data and Safety Monitoring Plan includes two institutional committees—the Data and Safety Monitoring Committee (DSMC) for non-phase 3 trials and the Data and Safety Monitoring Board (DSMB) for phase 3 randomized trials.
- These committees are essential for cancer centers like MSK, whose active portfolio includes over 800 clinical research protocols.
- In 2017, MSK created the Protocol Review Core (PRC) that provides centralized oversight and administration of MSK's protocol review committees, including DSMC and DSMB.
- DSMC and DSMB were centralized through PRC to optimize previously siloed processes. Based on portfolio size, PRC prioritized streamlining DSMC's processes and identified several areas for improvement.
- DSMC's current portfolio consists of 280 protocols, 266 of which are MSK Investigator Initiated Trials (IITs). Figure 1 outlines the portfolio by risk level.

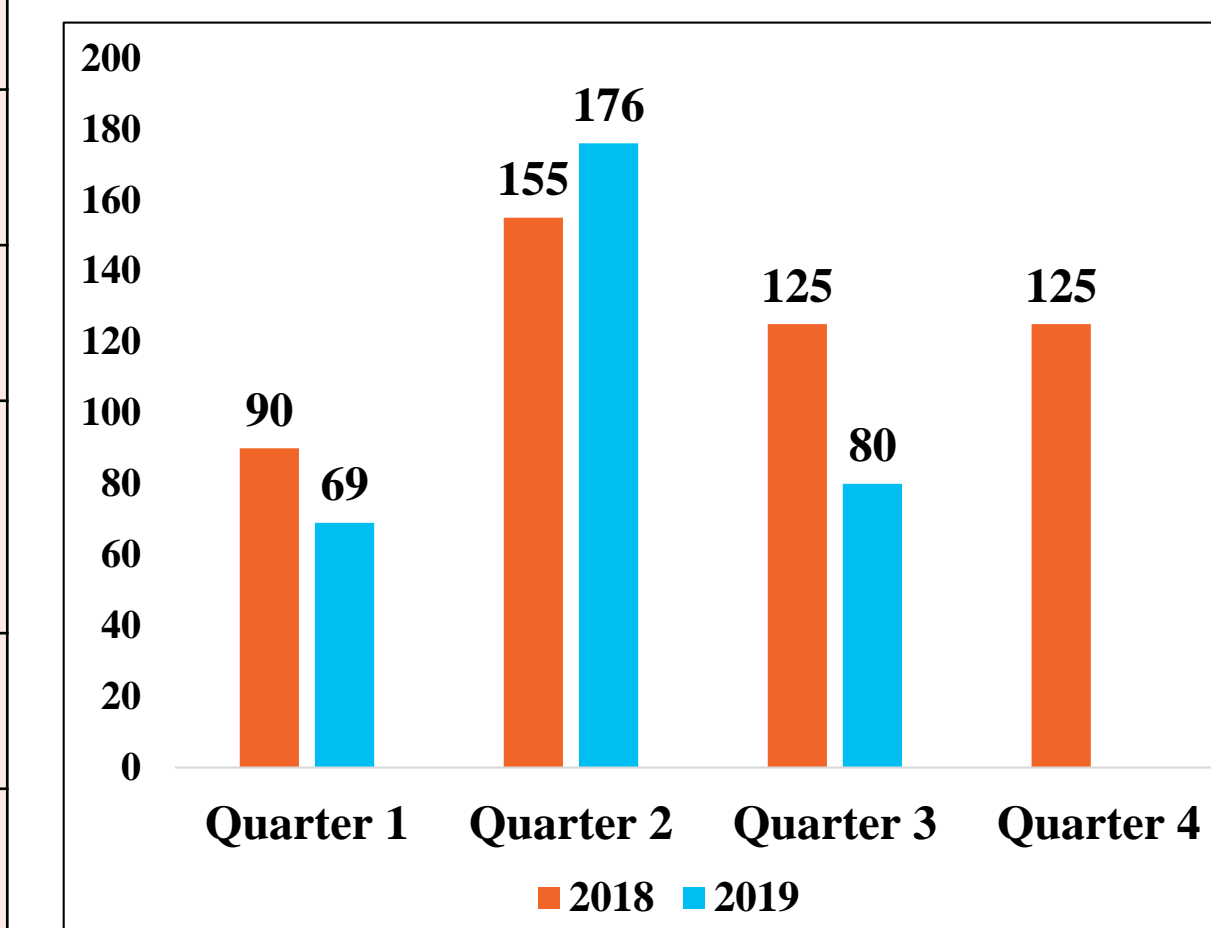
Changes Implemented

| | BEFORE | AFTER |
|-------------------------------------|--|---|
| Mission & Focus | <ul style="list-style-type: none"> Not clearly defined. Focused on study progress and accrual. | <ul style="list-style-type: none"> Focus on safety (unanticipated or excessive toxicity, protocol-specific stopping rules), data (completeness, accuracy, and database integrity), and progress and accrual. |
| Review Frequency | <ul style="list-style-type: none"> Quarterly meetings. Risk-based monitoring (high=quarterly, moderate=biannually, low=annually). | <ul style="list-style-type: none"> Added ad hoc meetings for flexibility. Risk-based monitoring is unchanged. Low risk focus is on interventional protocols. |
| Review Criteria | <ul style="list-style-type: none"> Monitored trials when external monitoring was less frequent than every 6 weeks. | <ul style="list-style-type: none"> Eliminated overlap with external monitoring. <ul style="list-style-type: none"> Eligible: MSK IITs and external protocols for which MSK is the data coordinating center. Ineligible: retrospective, biospecimen, specimen banking, and external protocols. |
| Protocol Identification | <ul style="list-style-type: none"> Local study teams & DSMC identified eligible protocols once opened to accrual (OTA). | <ul style="list-style-type: none"> Simplified identification of eligible protocols. Protocol Review Core identifies eligible protocols once OTA. |
| Monitoring Life Cycle | <ul style="list-style-type: none"> Monitoring initiated once a protocol OTA. Monitoring ends once closed to accrual (CTA). | <ul style="list-style-type: none"> Monitoring initiated following 1st accrual or 1 year after OTA if no accruals. Monitoring continues until no active participants. |
| Submission Requirements | <ul style="list-style-type: none"> DSMC Monitoring Form had limited open-ended questions and lacked flexibility for the different types of trials. | <ul style="list-style-type: none"> DSMC monitoring form revamped with questions to help identify potential issues. PI must provide more detail on matters such as serious adverse events, interim analyses, audits, etc. Protocol Review Core created tools to aid study teams in providing complete submissions. |
| Statistical Reviews | <ul style="list-style-type: none"> DSMC statistician did not conduct formal reviews. | <ul style="list-style-type: none"> Incorporated routine statistical reviews to evaluate stopping rules, interim analyses, amendment trends, etc. |
| Reviewer Checklist | <ul style="list-style-type: none"> Reviewer checklist was vague and lacked focus. | <ul style="list-style-type: none"> Updated reviewer checklist to ensure focus, detail, and consistency across reviews (Figure 2). |
| Reviewer Education & Experience | <ul style="list-style-type: none"> Limited to onboarding process. | <ul style="list-style-type: none"> Incorporated ongoing educational presentations into DSMC meetings. Initiated member surveys to improve engagement and satisfaction. |
| Inter-committee Communication | <ul style="list-style-type: none"> Infrequent communication between the DSMC and other institutional committees. | <ul style="list-style-type: none"> Increased communication with committees such as Institutional Review Board (IRB) and Protocol Review and Monitoring System (PRMS). |
| Leveraging Institutional Technology | <ul style="list-style-type: none"> Used MSK's home-grown web-based application called Protocol Information Management System (PIMS) for reviews, meeting minutes, and review letters. Submissions via email. | <ul style="list-style-type: none"> Enhanced PIMS to improve identification of eligible protocols, enable electronic submissions, optimize tracking, and allow for expedited reviews. Implemented inclusion of IRB/PRMS documents for DSMC reference within centralized review tab (Figure 3). |

Outcomes

- Simplified submission and review workflows are more efficient.
- Transparency has improved amongst DSMC and other institutional committees.
- For quarters 1-3, 2019 volume has decreased 12% compared to 2018 due to thoughtful monitoring criteria.
- 495 reviews were conducted in 2018 and 325 have been conducted in 2019 to date for quarters 1-3 (Figure 4).
- The decreased volume ensures reviewers can conduct efficient, comprehensive reviews.

Figure 4: DSMC Volume, 2018-2019



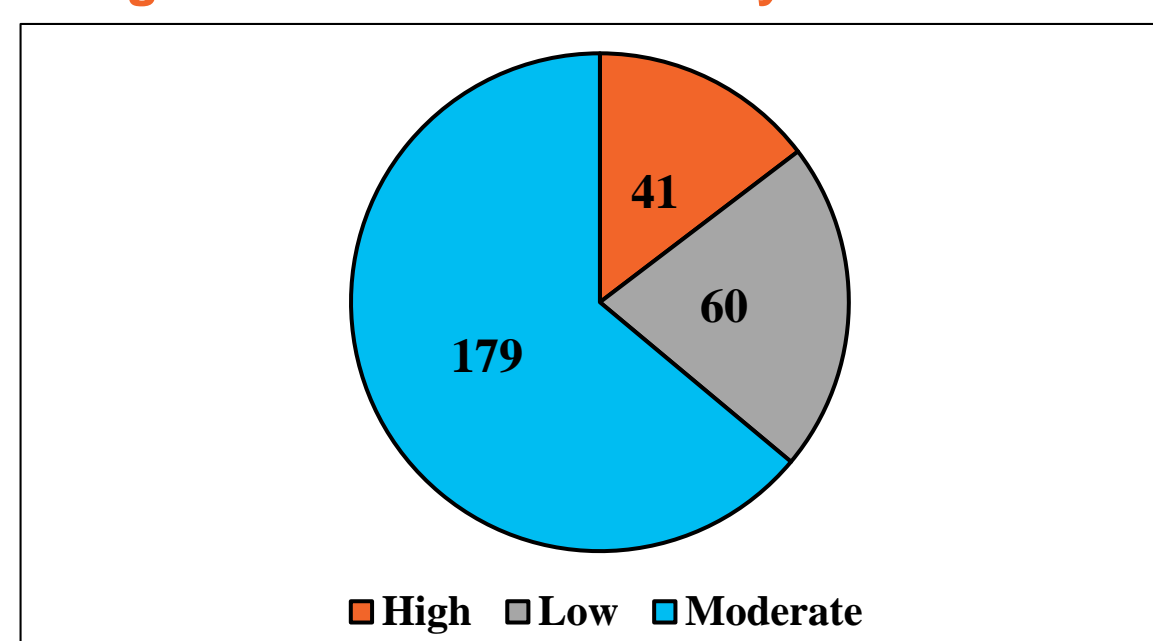
Conclusions

- The committee functions as an institutional service to investigators and study teams.
- DSMC communicates with IRB and PRMS for adequate portfolio management with minimal overlap.
- Processes, review requirements, and resources are clear and transparent.

Future Directions

- Streamline submission data requirements
- Incorporate data visualization
- Implement a DSMC charter and SOPs
- Additional PIMS enhancements
- Create educational materials

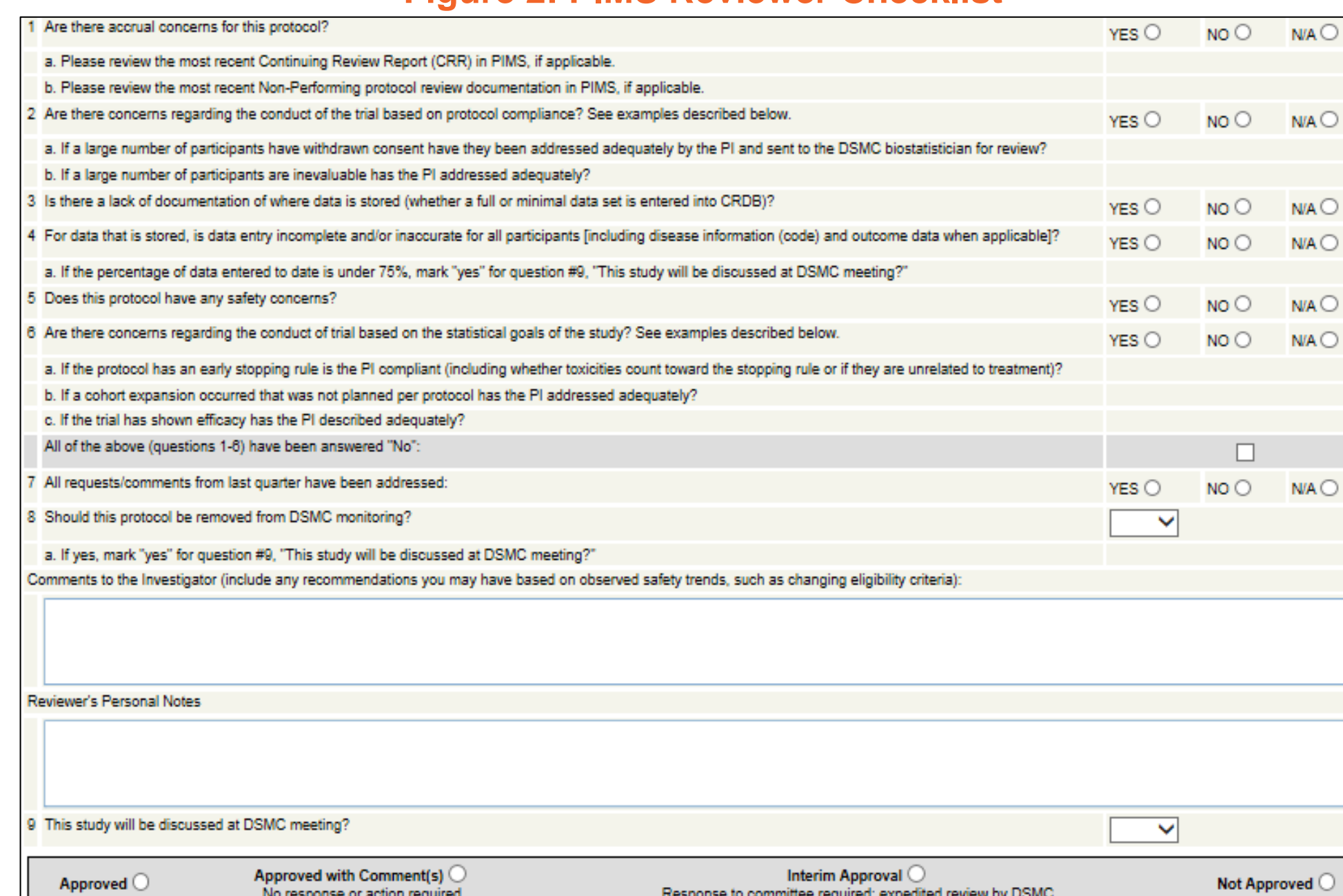
Figure 1: DSMC Portfolio by Risk Level



Goals

- Clarify monitoring criteria to appropriately identify protocols requiring DSMC oversight
- Update review processes
- Leverage technology to better coordinate DSMC reviews

Figure 2: PIMS Reviewer Checklist



1. Are there accrual concerns for this protocol? YES NO N/A

a. Please review the most recent Continuing Review Report (CRR) in PIMS, if applicable.

b. Please review the most recent Non-Performing protocol review documentation in PIMS, if applicable.

2. Are there concerns regarding the conduct of the trial based on protocol compliance? See examples described below. YES NO N/A

a. If a large number of participants have withdrawn consent have they been addressed adequately by the PI and sent to the DSMC biostatistician for review?

b. If a large number of participants are ineligible has the PI addressed adequately?

3. Is there a lack of documentation of where data is stored (whether a full or minimal data set is entered into CRDB)? YES NO N/A

4. For data that is stored, is data entry incomplete and/or inaccurate for all participants [including disease information (code) and outcome data when applicable]? YES NO N/A

a. If the percentage of data entered to date is under 75%, mark "yes" for question #9, "This study will be discussed at DSMC meeting?"

5. Does this protocol have any safety concerns? YES NO N/A

6. Are there concerns regarding the conduct of trial based on the statistical goals of the study? See examples described below. YES NO N/A

a. If the protocol has an early stopping rule is the PI compliant (including whether toxicities count toward the stopping rule or if they are unrelated to treatment)?

b. If a cohort expansion occurred that was not planned per protocol has the PI addressed adequately?

c. If the trial has shown efficacy has the PI described adequately?

All of the above (questions 1-6) have been answered "No"

7. All requests/comments from last quarter have been addressed: YES NO N/A

8. Should this protocol be removed from DSMC monitoring?

a. If yes, mark "yes" for question #9, "This study will be discussed at DSMC meeting?"

Comments to the investigator (include any recommendations you may have based on observed safety trends, such as changing eligibility criteria):

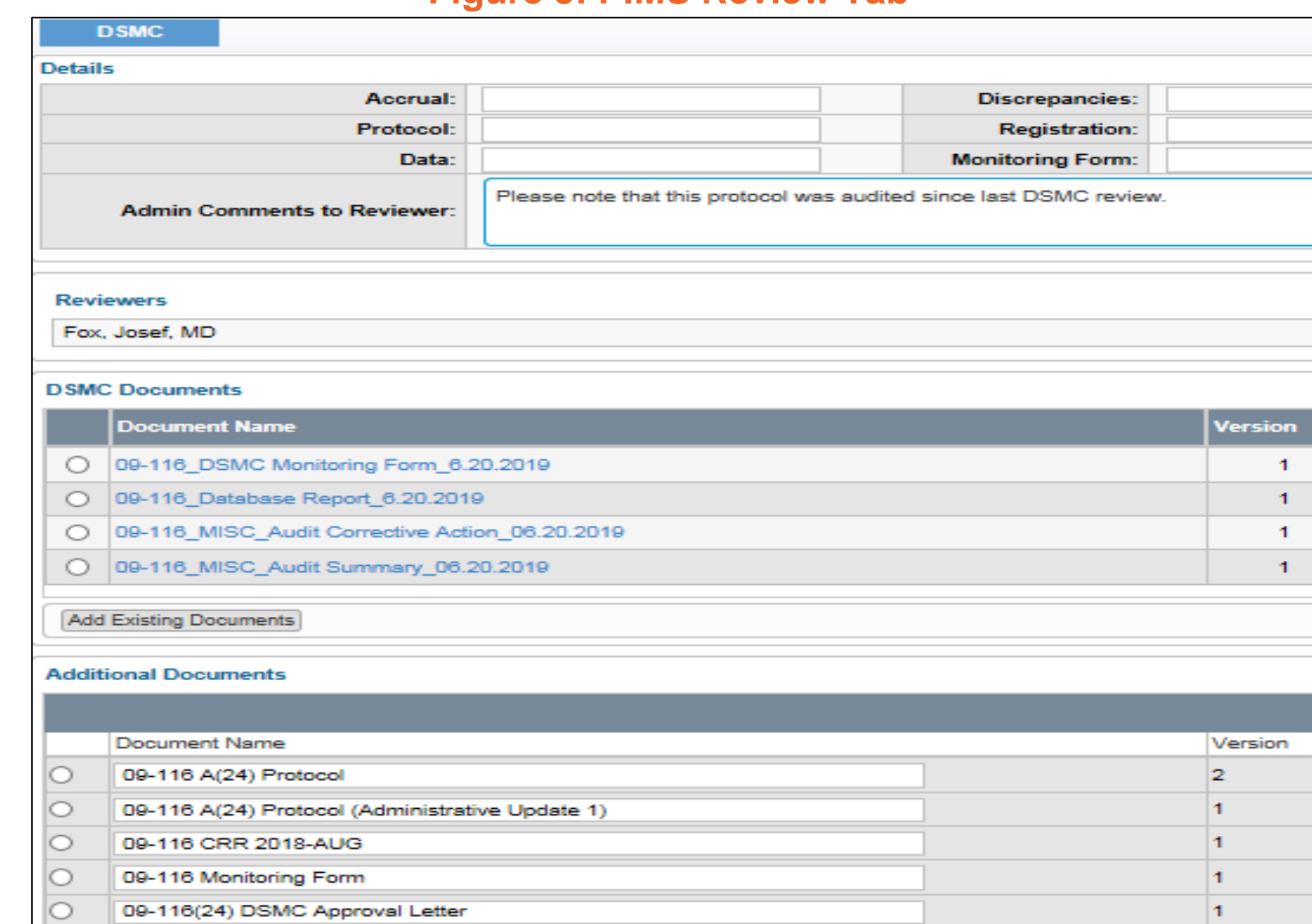
Reviewer's Personal Notes

9. This study will be discussed at DSMC meeting?

Approved Approved with Comment(s) Interim Approval Not Approved

No response or action required Response to committee required: expedited review by DSMC

Figure 3: PIMS Review Tab



DSMC

Details

Accrual: Discrepancies:

Protocol: Registration:

Data: Monitoring Form:

Admin Comments to Reviewer: Please note that this protocol was audited since last DSMC review.

Reviewers: Fox, Josef, MD

DSMC Documents

| Document Name | Version |
|--|---------|
| 09-116_DSMC Monitoring Form_6.20.2019 | 1 |
| 09-116_Database Report_6.20.2019 | 1 |
| 09-116_MISC_Audit Corrective Action_06.20.2019 | 1 |
| 09-116_MISC_Audit Summary_06.20.2019 | 1 |

(Add Existing Documents)

Additional Documents

| Document Name | Version |
|---|---------|
| 09-116 A(24) Protocol | 2 |
| 09-116 A(24) Protocol (Administrative Update 1) | 1 |
| 09-116 CRR 2018-AUG | 1 |
| 09-116 Monitoring Form | 1 |
| 09-116(24) DSMC Approval Letter | 1 |