Category: Trial Start-up, Activation, Regulatory, and Protocol Development – Completed project

Comparison of Protocol Review and Monitoring System (PRMS) Operations at a Standalone Versus a Matrixed Cancer Center

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1. Background

- The National Cancer Act of 1971 formalized the National Cancer Institute (NCI) as an operating division within the National Institutes of Health.
- This paved the way for the current 72 NCI-Designated Cancer Centers across the U.S, who earn and maintain designation by meeting requirements for the NCI P30 Cancer Center Support Grant (CCSG).
- Among the first to receive this designation were Memorial Sloan Kettering Cancer Center (MSK) in 1971 and Mayo Clinic Comprehensive Cancer Center (MCCCC) in 1973.
- To maintain this designation, each center must assure rigorous scientific oversight of all cancer clinical trials via a structured Protocol Review and Monitoring System (PRMS), a core component of CCSG guidelines since 2014.
- While MSK operates as a standalone center and MCCCC functions as a matrixed center within the Mayo Clinic, both centers maintain structured PRMS workflows.

2. Goals

To compare PRMS operations and CCSG guideline interpretations between MSK and MCCCC, identifying operational similarities, differences, and opportunities for collaboration to enhance PRMS effectiveness.

3. Solutions and Methods

- PRMS staff from both centers formed a working group.
- Weekly meetings and a shared document facilitated detailed workflow comparison.
- Initial discussions consisted of comparing institutional structures (standalone versus matrixed).
- Comparisons were structured using core PRMS focus areas identified by the group:
    1. Organization and Support Structure
    2. Prioritization
    3. Stage 1 Review
    4. Stage 2 Review
    5. Performance Monitoring
    6. Technology Leveraged

4. Outcomes

- The working group created a network between the centers, fostering ongoing collaboration and strategic alignment in PRMS operations.
- We facilitated knowledge sharing by discussing workflows related to CCSG guideline interpretation and generated a comparative table (Table 1) across the focus areas resulting in shared insights:
    - Differences in reporting and organizational structures reflect the inherent differences between matrixed and standalone centers.
    - Both rely on disease experts to prioritize trials to manage portfolio volume and drive activation timelines.

- CCSG guidelines indicate stage 1 should be disease or discipline specific, providing flexibility. MSK's discipline-focused approach contrasts with MCCCC's disease-specific model. Each model aligns with each center's organizational structure.
- CCSG guidelines outline specific stage 2 requirements, therefore both have similar stage 2 review structure with minimal variation.
- CCSG guidelines require continuous monitoring of open studies for accrual progress, new safety information, and scientific relevance. Both leverage accrual data to identify underperforming trials with each employing a nuanced approach to adapt to differing operational contexts.
- MSK and MCCCC leverage digital tools to ensure PRMS efficiency.

5. Lessons Learned and Future Directions

Lessons:

- MSK and MCCCC demonstrate a similar interpretation of CCSG guidelines. Operational similarities are anchored in CCSG guidelines with differences attributed to the standalone versus matrixed organizational structures.
- Understanding operational differences enhanced mutual respect and appreciation, boosting collaboration and relationship building. This also led to non-PRMS meetings between the centers about activation and amendments.

Future Directions:

- Conduct in-depth performance monitoring analysis and share ideas for process improvements and efficiencies.
- Engage PRMS leadership to foster a collaborative network.
- Develop shared educational resources to improve PRMS functions at both centers.
- Collaborate on technological advancements for data optimization, visualization, reporting, and overall process automation.

Figure

Focus	Memorial Sloan Kettering Cancer Center (MSK) STANDALONE	Mayo Clinical Comprehensive Cancer Center (MCCCC) MATRIXED	Insights Gained
Organization and Support	**Reporting Structure:** PRMS → SVP of Clinical Research → Physician Executive → CEO **PRMS Leadership:** 1 overall PRMS chair oversees stage 2 and Performance Monitoring committees. • Stage 1: Each committee has designated chair and co-chairs • Stage 2: 6 co-chairs – 1 biostatistical co-chair **Clinical Research Structure:** Clinical Research Administration (CRA) includes 2 groups, Clinical Research Operations and Clinical Research Compliance. The Protocol Activation, Review & Human Research Protection Program (HRPP) Unit within Clinical Research Compliance includes the Protocol Review Core (PRC), the team who manages MSK's PRMS. **PRMS Team:** PRC is a team of 12 – 1 Associate Director, 4 program managers, 6 protocol review managers, 1 senior project manager (manages PRMS stage 1 and 2 and DSM Committees). *PRC reports up to our unit's Senior Director and Vice-President, Research Compliance.* **Portfolio Volume:** Between 2021-2023, MSK activated a median of 291 prospective new protocols per year and monitored a prospective portfolio of ~1000. **Catchment Area:** Includes 23 counties across New York, New Jersey, and Connecticut, nearly 21 million people of diverse backgrounds.	**Reporting Structure:** PRMS → Deputy Director for Cancer Clinical Research → MCCCC's Executive Director → Mayo Clinic President and CEO **PRMS Leadership:** 1 overall PRMS chair oversees two-stage scientific review and performance monitoring and partners with Deputy Director for Cancer Disease Groups (DG). • Stage 1: Each DG has a designated chair and may have co-chairs • Stage 2: 4 chairs and co-chairs **Clinical Research Structure:** The Cancer Clinical Trials Office (CCTO) includes the PRMS Administrative Team, Activation, Regulatory, Data Safety Monitoring (DSM), and Compliance teams for cancer clinical trials. Mayo Clinic IRB is shared between cancer and non-cancer trials. **PRMS Team:** There are 18 staff supporting DG stage 1 review; PRMS Administrative Team is team of 3 – 1 program manager, 1 program coordinator, and 1 administrative assistant to support stage 2 review and monitoring. **Portfolio Volume:** Between 2021-2023, MCCCC activated a median of 228 new cancer protocols and monitored a prospective portfolio of ~1000. **Catchment Area:** MCCCC's 3 geographic designated centers serve vastly different areas in 75 counties across Arizona, Florida, and the Midwest (Minnesota, Wisconsin, and Iowa).	The reporting and organizational structures reflect the inherent differences between matrixed and standalone centers. • MSK's streamlined structure contrasts with MCCCC's more complex organization, reflecting the broader Mayo Clinic structure and leadership that oversees both cancer and non-cancer activities. • PRMS leadership structure and portfolio volume is similar but the teams who manage each PRMS differ. MSK's PRC team manages all reviews within stage 1 and stage 2 while MCCCC relies on the DGs to manage stage 1 review while the PRMS Administrative Team focuses on stage 2 review and monitoring. • MSK's catchment area is in a central geographic location that includes a diverse population while MCCCC's 3 geographic designated centers and catchment areas add complexity to MCCCC's operations. Both Centers have unique opportunities to tailor their portfolio to meet the needs of diverse populations.
Prioritization	**Stage 1:** Numerical (5-point) protocol categorization system is assigned by department/service leadership prior to submission for stage 1 review. System is used for high volume groups. Annual allocations by category provided to each department/service. **Stage 2:** Scope of evaluation is programmatic fit and scientific importance.	**Stage 1:** Considers disease group portfolio, focusing solely on cancer trials portfolio. **Stage 2:** Numerical (5-point) protocol categorization system is assigned by PRMC considering full portfolio. No annual allocations by category.	Shared reliance on disease experts to prioritize trials and manage portfolio volume and activation timelines. Sponsoring Departments/Services/Disease Groups are responsible for managing their own portfolios while placing limits based on available resources. • MSK's approach allows for stage 1 prioritization by requiring priority category to be provided prior to stage 1 reviews. • MCCCC's approach offers adaptive benefits by prioritizing within the disease-specific portfolio during stage 1 review and re-prioritizing for the full center portfolio during stage 2 review.
Stage 1 Review	**Overview:** Includes departmental, regulatory, and feasibility committees. Committee determination form is leveraged to identify required committees and level of review. **Departmental/Disease Groups:** Departmental committees (21) are discipline/modality specific (e.g., Medicine, Surgery, etc.). Biostatistics departmental committee reviews MSK IITs only. Feasibility is within scope of these reviews. **Regulatory:** Included within PRMS structure and occur in parallel to stage 1 and 2 reviews. **Feasibility:** Additional operational reviews conducted within defined scope (e.g. multicenter, OneMSK, etc) but do not assess overall study feasibility.	**Overview:** Includes Cancer DGs, operational reviews, centralized Preparation Team, and Feasibility Committee. PRMS intake Form is leveraged to determine level of review required by respective committees. **Departmental/Disease Groups:** Multidisciplinary, multi-site Cancer DGs (15) collaborate with institutional departments (i.e., cancer and non-cancer). Biostatistical reviews embedded within the DGs. **Regulatory:** Regulatory committees are ancillary to PRMS review structure and inform Feasibility Committee review. **Feasibility:** Committee assesses overall study feasibility considering stage 1 reviews and can defer studies back to DG based on feasibility concerns.	CCSG guidelines provide flexibility by indicating stage 1 should be disease or discipline specific. MSK's discipline-focused approach contrasts with MCCCC's disease-specific model. • Regulatory reviews are centralized within MSK's PRMS but function as ancillary committees to MCCCC's PRMS. • MCCCC has a centralized feasibility review with the option of deferring studies while MSK conducts multiple feasibility reviews that are specific in scope and ongoing throughout the activation process.

Stage 2 Review	**Frequency:** Weekly Research Council (RC) committee meetings.
	
	Composition: 60 junior and senior multidisciplinary members, including 5 PhD level statisticians. Minimal overlap with IRB and DSM membership.
	
	Assignments & Review Types: Varies based on trial design. Conflicts of Interest (COI) considered for review assignments. Some studies are expedited (e.g., external PRMS of record, expanded access, epidemiologic, etc.).
	• New Protocols: 2 scientific reviewers (1 for phase 3), 1 statistical reviewer for externally sponsored studies.
	• Amendments: 1 scientific reviewer, 1 statistical reviewer – reviews conducted outside meeting.
	
	Voting: Formal voting but no quorum requirements. Majority vote determines meeting action. Abstentions applicable for COIs.
	
	IRB Review Flow: Parallel PRMS and IRB reviews for industry sponsored, priority 1 studies where MSK is the IRB of Record (IoR).
		Frequency: Weekly Protocol Review and Monitoring Committee (PRMC) committee meetings.
		
		Composition: 40 junior and senior multidisciplinary members, including 5 statisticians. 16 ad hoc reviewers who do not vote or count toward quorum. No overlap with IRB and DSM membership.
		
		Assignments & Review Types: COI is mitigated for all reviewers. Some studies are administratively reviewed by the PRMS Chair (e.g., externally peer-reviewed, cooperative group, etc.). All full reviews receive 1 scientific reviewer and 1 statistical reviewer with IITs requiring PhD-level statistical reviewer.
		
		Voting: Formal voting and quorum is required to conduct a final vote. Majority vote determines meeting action. Abstentions applicable for COIs.
		
		IRB Review Flow: MCCCC PRMS and Mayo Clinic IRB do not conduct parallel reviews. Mayo Clinic IRB will complete pre-screening during PRMC review only.
			CCSG guidelines outline specific stage 2 requirements and responsibilities, resulting in similar stage 2 review structure and scope.
			• Implementation of membership requirements to meet unique needs of each Center results in variability such as:
			  ○ MCCCC utilizes ad hoc members to supplement reviews and vary committee expertise without impacting meeting quorum requirements. MSK does not have ad hoc members; all reviewers are full members of the committee.
			  ○ MSK requires PhD level statisticians while MCCCC uses a mix of master's and PhD level statisticians, depending on complexity of reviews.
			• MSK has slightly larger membership. The goal is to reduce member workload with a median of 9 new protocols reviewed per reviewer in 2023. MCCCC workload was a median of 5 new protocols per reviewer in 2023.
			• As a standalone Cancer Center, MSK's IRB is cancer specific. MCCCC has a matrixed structure and uses Mayo Clinic's IRB which creates unique challenges for conducting parallel reviews such as competing with non-cancer portfolio and deferring to PRMC for cancer-specific review.

Performance Monitoring	**Structure/Composition:** Performance Monitoring Committee (PMC) is a sub-committee of Research Council (stage 2) and includes 11 committee members from varying clinical backgrounds. **Frequency:** Two monitoring tracks: continual and annual. • Continual monitoring: Occurs monthly. Criteria = 0 accruals in >6 months • Annual monitoring: Criteria = Estimated time to completion >5 years; Open to accrual >5 years. Adjusted criteria for pediatric and NCTN studies. **Exemptions:** PMC adjusts monitoring frequency, as needed, including exempting from monitoring for pre-specified periods of time. PMC exempts certain studies from routine monitoring (e.g., rare disease).	**Structure/Composition:** Performance monitoring reviews conducted by PRMS Chair and PRMC (stage 2) chairs/co-chairs rather than a separate committee. **Frequency:** One monitoring track (continual) occurs monthly. Trials monitored based on accrual progress at set timepoints. Criteria and timepoints differ for Phase I, non-Phase I, Pediatrics, and Rare (<5/100,000 incidence) clinical trials. **Exemptions:** PRMC chairs do not adjust monitoring frequency for studies and do not exempt studies from routine monitoring.	Accrual data is leveraged to identify underperforming trials and review accrual progress, new safety information, and scientific relevance. Approaches vary to adapt to differing operational contexts. • MSK's approach is more flexible with ability to adjust a study's monitoring frequency; since criteria are applied broadly across all studies whereas MCCCC has a customized approach with different criteria based on study phase, rarity, and pediatrics so monitoring frequency is not adjusted. • MCCCC's multiple geographic centers add complexity to performance monitoring because monitoring takes place at both the site and study level whereas MSK locations are considered part of one site.
Technology	**PRMS System:** An in-house developed web-based application called Protocol Information Management System (PIMS). **Functions:** Used throughout activation and review process including stage 1, stage 2, IRB, and DSM committees; submitting/accepting submissions, conducting reviews, taking meeting minutes, drafting and sending review letters, reporting. Leveraged for electronic regulatory binder, protocol auditing and	**PRMS System:** Homegrown REDCap-based system, Velos eResearch, and Florence eBinder. Systems combine via centralized visualization dashboards and reports. **Functions:** REDCap-based system used for two-stage scientific review, Velos eResearch used for all other protocol lifecycle management, accrual monitoring, and DSM activities for cancer clinical trials. Florence eBinder is used for regulatory activities.	Digital tools are leveraged, and technology is adapted for PRMS-specific workflows to ensure PRMS efficiency. • MSK's home-grown integrated system highlights the importance of customizable solutions in managing complex PRMS workflows with minimal manual work. • MCCCC requires interface with broader Mayo Clinic systems. • Opportunities for technology-driven enhancements exist for both Centers, specifically related to data visualization and reporting.