SAVAC Cross-Reactive Assay Technical Advisory Working Group

1 June 2025, Brisbane, Australia

Attendees:

- **In-person:** Tom Parks (Chair), Reuben McGregor (Secretary), Madeleine Cunningham, Allan Saul, Nina van Sorge, Jerome Kim
- **Online:** James Dale

Purpose

The Cross-Reactive Assay Technical Advisory Working Group (TAWG) was established to guide stakeholders on the role of assays designed to detect cross-reactive immune responses following the administration of Group A Streptococcus (GAS) vaccines. The group's overarching aim is to inform the development of safe and effective vaccines by providing clear, practical, and evidence-based guidance for early-phase safety monitoring.

Overall Summary of Discussion

The meeting served as the foundational session for the TAWG, successfully establishing a clear roadmap. The discussion cantered on defining the group's scope and key outputs, debating the utility of various safety assays, and outlining a strategy for regulatory engagement. Key topics included:

- Finalizing the working definition of "cross-reactivity" to ensure a clear and focused scope.
- Debating the need for and scope of a systematic literature review to formally assess the current landscape of cross-reactivity assays.
- The universal agreement on the lack of an established "gold standard" assay and the limitations of historical methods.
- Formulating a forward-looking strategy to shift from subjective, historical assays (e.g., immunofluorescence on tissue) toward modern, objective, high-throughput technologies.
- Discussing practical considerations for clinical trials, including participant screening and the importance of measuring change from baseline.

Detailed Discussion Points

- **Defining "Cross-Reactivity":** The group refined the initial definition based on feedback. The final agreed-upon definition is:

"The development of an immune response due to vaccination that binds to human tissue in a manner that could indicate autoimmune sequelae associated with GAS infection."

- **Defining the TAWG's Scope:** A key discussion point was whether to include biomarkers of general autoimmunity (e.g. other immune signatures) in the group's remit. General agreement that that to remain effective, the group should maintain a narrow focus on ***antibody-mediated cross-reactivity***.
- **Systematic Review:**
    - There was a strong consensus that a formal, independent systematic review is needed.
    - The primary goal of the review is not to find the perfect assay, but to formally document with methodological rigor that: ***no "gold standard" assay with known performance characteristics currently exists***. This provides the evidence base for the group's recommendations.
    - The review could be framed by two key questions:
        1. Is there a gold standard assay to detect vaccine-induced auto-reactivity after Strep A vaccination?
        2. How has this issue been addressed for other vaccines or with the use of novel adjuvants?
    - The review must be commissioned to an external party to maintain objectivity.
- **Historical Assays:**
    - Immunofluorescence assays on frozen tissue sections has historically been used as a safety measure and accepted by the FDA.
    - Agreement that this method, while a historical precedent, ***is subjective, cumbersome, and not practical for larger, later-phase clinical trials.***
- **A New Strategic Direction for Assays:**
    - One option discussed was a shift the strategic focus. The goal is **not** to find a perfect diagnostic biomarker for Acute Rheumatic Fever (ARF).
    - Instead, the group could suggest the development of a modern, unbiased, high-throughput assay to generate a quantitative **"auto-reactivity score."**
    - This score would be used to detect a safety signal by ***objectively comparing pre- and post-vaccination samples in Phase 1 trials***.
- **Clinical Trial Practicality:** The group discussed the practice of pre-screening trial participants. James Dale noted that in his experience, only one individual was ever excluded due to pre-existing auto-antibodies. The consensus was that excluding participants is less important than establishing a baseline and measuring the ***change in auto-reactivity*** post-vaccination.
- **Strategy for Regulatory Engagement:** The group discussed the best way to interact with regulatory bodies. The consensus was to develop a proactive strategy: instead of asking regulators for open-ended guidance, the TAWG could use its findings (from the systematic review and expert opinion) to formulate a proposed framework and a set of precise questions. This package could then be presented to a convened panel of regulatory experts for feedback?

Decisions & Key Outcomes

1. **Finalized Definition:** The group formally adopted the refined definition of cross-reactivity.
2. **Narrow Scope Confirmed:** The TAWG will focus exclusively on antibody-mediated cross-reactive assays.
3. **Systematic Review:** A formal, externally-commissioned systematic review will be initiated to document the lack of a gold-standard assay.
4. **Expert Opinion Piece:** The TAWG will author an expert opinion piece to accompany the systematic review and outline its strategic recommendations.
5. **Strategic Shift Endorsed:** The group endorsed a move away from historical tissue-based assays towards the development of modern, quantitative, high-throughput methods for safety screening.
6. **Proactive Regulatory Strategy:** The group agreed on a proactive approach for engaging with regulators, cantered on presenting a well-defined framework and specific questions to an expert panel.