The SMSRF 5-Year Research Roadmap: From RAI1 Biology to Clinical Development
A Plain-Language Guide to What Comes Next
June 2026

For families living with Smith-Magenis syndrome (SMS), it can sometimes feel like progress moves slowly—especially when you are dealing with daily challenges like sleep disruption, behavior, learning differences, and health complications. But we want to share something important: SMS research is reaching a new turning point.

Over the last fifteen years, SMS Research Foundation (SMSRF) investments have helped validate a major scientific idea that could change what is possible for our community: boosting RAI1 may be able to improve (and potentially reverse) key SMS challenges.

RAI1 is the gene that is most often missing or not working properly in SMS. Early lab studies now strongly support a hopeful premise: if we can safely increase RAI1 output in the brain, we may be able to reduce core symptoms and improve functioning. That is why SMSRF considers RAI1-focused therapies a "north star" for disease-modifying treatment.
At the same time, we want to be honest: developing new therapies is still high-risk and complex, especially when it involves the brain. SMS is also behind other single- gene neurodevelopmental conditions - like Angelman syndrome and Rett syndrome - that already have multiple clinical trials underway.

That gap is real—but so is the opportunity.

Why This Moment Matters
Even though SMS has no disease-modifying clinical trials yet, the overall environment is shifting in our favor. Over the next five years, we believe there is a clear path to *accelerate progress*—and bring SMS much closer to meaningful clinical trials.

Here is what is changing:
1) Our community is becoming trial-ready
The SMS community is more organized than ever. A PRISMS-led registry is active and growing, capturing natural history information about SMS over time. This type of data is essential for future trials because it helps define baseline patterns (like sleep, behavior, medical issues, and development) and makes it easier to recruit families quickly and fairly.
Importantly, that registry is preparing for improvements—and SMSRF is exploring partnership opportunities to help make it:

- easier for families to use.
- more complete and higher quality
- more useful for researchers and future study sponsors
- better aligned with regulatory requirements

Trial readiness is not just a concept anymore. It is our goal to make it real.

2) Regulators are creating clearer pathways for advanced therapies
The FDA is actively updating guidance for cell and gene therapies and highlighting ways sponsors can engage earlier and potentially use accelerated pathways for promising treatments. Separately, there is growing momentum in Congress to restore the Rare Pediatric Disease Priority Review Voucher program. In plain terms, this program can make rare pediatric therapies more financially attractive to companies—because an approved therapy can come with a "voucher" that may be sold or used for faster review of another drug. That kind of incentive can increase industry interest in rare diseases like SMS.

3) "N-of-few" precedents are making ultra-small trials more feasible
In 2023–2025, there were landmark cases where personalized gene-editing treatments were given to individual children under compassionate use. These examples helped normalize the idea that even "N-of-1" or "N-of-few" studies (Studies with very small numbers of participants)—can be possible for rare diseases, when the science and safety case is strong enough.

4) Funding for rare pediatric genetic disorders is expanding
Major funders and government programs and large philanthropic initiatives are investing in enabling technologies—especially around in vivo genetic medicines, delivery systems, and scalable platforms. These investments will not all target SMS directly, but they create tools and partnerships that could "spill over" into SMS research if we position ourselves well.

5) Brain delivery tools are improving
A core hurdle for SMS therapies is this: how do we safely deliver treatment across the brain?
The field is advancing quickly with:

- new Adeno-associated virus (AAV) vectors – the leading, non-pathogenic, non-integrating tools for in vivo gene therapy - that may cross the blood-brain barrier more effectively
- non-viral delivery (like specialized nanoparticles and lipid nanoparticles)
- better manufacturing and analytics that lower barriers for small organizations

By the time SMS therapies are ready for human studies, our toolkit may be far better than what was available just a few years ago.

6) Brain atlases + AI are accelerating what we can measure
New large-scale brain mapping projects are creating extremely detailed atlases of brain development—showing where and when different genes matter across thousands of cell types. When combined with AI, these tools could help identify:

- the best window for intervention
- the best biomarkers - measurable indicators of normal biological processes - and endpoints for trials
- how to detect treatment effects sooner and more clearly

What Therapies Are in View for SMS – Possible Paths for Disease-Modifying Approaches
1) Gene activation (like CRISPRa)
These approaches aim to increase RAI1 activity from the remaining working copy of the gene—without changing the DNA sequence. They may also allow more precise control of expression (which matters because too much RAI1 could cause harm). This is the approach most directly supported by current SMS-specific data, and it is the focus of SMSRF's flagship work.

2) RNA or translation boosting
RNA is a nucleic acid present in all living cells. Its principal role is to function as a messenger carrying instructions for controlling the synthesis of proteins. RNA or translation boosting involves technologies designed to increase protein production from specific messenger RNAs (mRNAs) by enhancing their translation efficiency. The science is earlier-stage, but it is an intriguing possibility for future work.

3) Gene replacement
Classic gene therapy approaches work well in some disorders, but RAI1 is a particularly complicated gene because of its size and the need for careful expression control. Still, new technical approaches could make this viable over time, so SMSRF will continue monitoring this space.

What About Improving Life Now?
While disease-modifying therapies are the long-term goal, families also deserve progress that helps *today*. SMSRF is exploring whether it makes sense to also support near-term symptomatic interventions that can improve quality of life and strengthen future trial measurement systems.
Examples could include:

- Drug repurposing (testing existing medicines for SMS symptom domains)
- Sleep and neuromodulation pilots (where evidence is emerging, but more data is needed)
- Supportive metabolic/oxidative approaches in which medical, dietary, or lifestyle strategies aimed at optimizing how the body generates energy and neutralizing harmful oxidative stressors
- Appetite/weight management tools, including GLP-1 medications, which have shown promising outcomes in at least one SMS case report (including possible behavioral improvements)

These strategies would not replace disease-modifying work—but they could provide meaningful help sooner and reduce hidden variables in later trials.

What Happens Next: SMSRF's Five-Year Strategy
To move faster, SMSRF will focus on three core priorities:

1) Build an organized initiative to bridge the gap between specialized scientific research and the public. That means proactively recruiting:

- experts in gene activation and expression control
- leaders in CNS delivery
- trial-experienced clinicians and sites
- teams with proven histories in related syndromes (Angelman, Rett for example)

Instead of waiting for researchers to come to SMS, we will find the best teams and bring them in.

2) Shift toward milestone-based funding
We want funding to be clearer, more strategic, and faster-moving—Advancing projects based on measurable progress with defined go/no-go criteria (e.g., "RAI1 activation," "brain delivery," "biomarkers," "Investigational New Drug(IND)-enabling package"). This approach helps reduce the risk of spending years on programs that are not working.

3) Make "trial readiness" real
Being clinical trial ready means having the necessary infrastructure, trained staff, validated tools, and identified patient cohorts prepared to initiate a study efficiently. For SMS, we must strengthen the registry and natural history data so that when a therapy is ready, the community can move fast.

Our North Star: A First-in-Human Disease-Modifying Trial by ~2030
SMSRF's goal is ambitious but realistic: support the field toward a first-in-human disease-modifying SMS trial by 2030, while staying flexible on the exact therapeutic modality. While this timeline may shift depending on the science, it creates a targeted goal for all of us to work together towards.

A representative timeline looks like:

- ~2027: strong proof-of-concept results in animals
- 2028–2029: Investigational New Drug - IND-enabling safety and biodistribution studies
- ~2029: IND submission
- ~2030: first dosing in an early Phase 1/2 trial

What This Means for Families

This roadmap is not just a scientific document. It is a commitment to build the foundation needed for real therapeutic progress. In the next year, families may see:

- more active outreach to researchers and clinical partners
- new opportunities to participate in registry improvements
- pilot studies designed to strengthen measurement tools
- clearer communication about therapeutic strategies and milestones

Most importantly: the SMS community is closer than ever to being a true clinical-development ecosystem.

Looking Ahead

There is a great deal of work to do—and there will be obstacles. But the scientific foundation is stronger, the external environment is improving, and the community is more ready than ever. SMSRF believes that with focused strategy and the right partnerships, the next five years can be the period when SMS transitions from “promising science” to real clinical programs.

The next five years can be the period when SMS moves from promising science into clinical programs. But it will take a community-wide commitment to build the infrastructure, partnerships, and funding required. Together, we can bring disease-modifying treatments for Smith-Magenis syndrome within reach.

We will keep you updated every step of the way.