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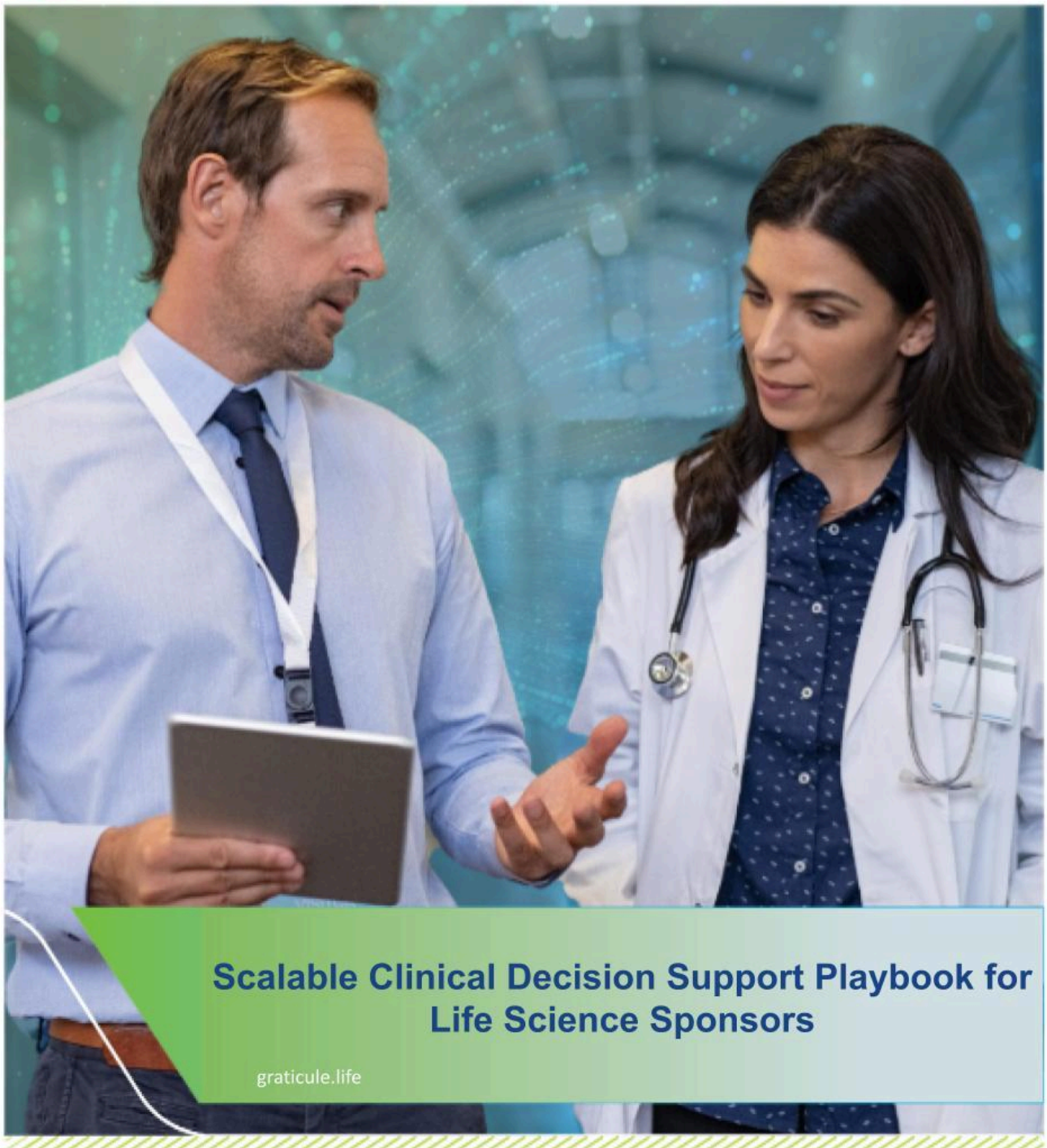
White Paper



Scalable Clinical Decision Support Playbook for Life Science Sponsors

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Executive Summary

Graticule provides “Patient Finder” solutions to life sciences clients seeking to reduce care gaps that limit patient access to approved interventions. Care gaps limit adoption of beneficial new medical therapies after the products are approved by the FDA. For example, there may be no easy way to identify patients with a rare disease with a long diagnostic odyssey even after a therapy is approved to slow the progression of the disease. Another use case is if a second line drug is only appropriate once patients have failed a first line therapy. But because there aren’t systems in place to detect first line failure the patients who have ongoing symptoms rarely receive testing or evaluation for moving to the second line option.

This playbook answers questions often asked of Graticule about how we approach these solutions. The most common question asked to us is “How can a technology solution for offering decision tools to health systems be scaled beyond a single collaborator?” But we also have to answer additional questions including:

- How do we (sponsor, Graticule, and site) manage the business relationships with each other?
- When are these projects considered research? Do we need a research protocol?
- What are the steps and phases we take?

The opportunity to advance care with CDS

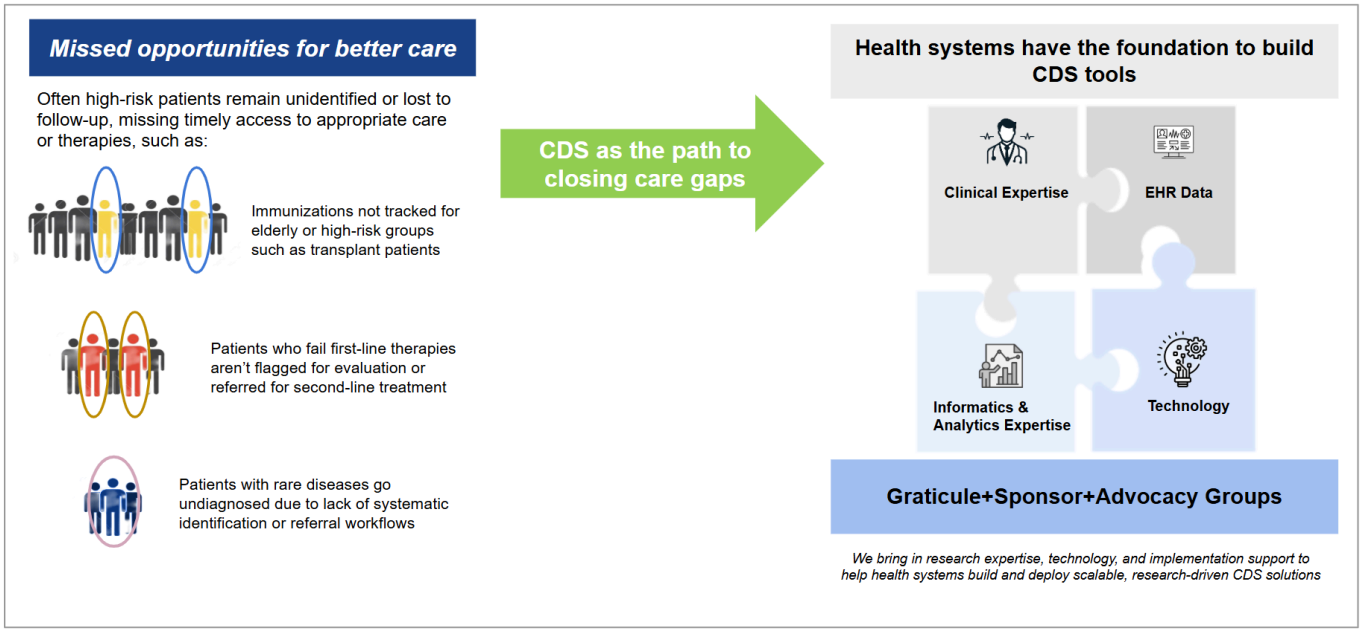
Despite guidelines and peer reviewed best practices more needs to be done to support physicians to provide better care and to translate the large investments life sciences make into generating evidence into medical practice at the point of care.

Most health systems now have adopted enterprise wide Electronic Health Records (EHR) systems with mature implementations. Through much evolution and government encouragement these tools have open tool kits such as FHIR, data warehouses, and developer APIs available to companies such as Graticule for building plug-in applications. But health systems don’t have sufficient incentives or available budgets to build custom logic, processes, and timely prompts such as alerts or order sets to address the hundreds or thousands of potential care gaps that medicine can address. As a result translating evidence into practice can be harder than it could be if such tools could be ethically built, tested, and distributed

We have arrived at a point in time where it is possible and practical for sponsors to make central investments across health systems by generating utilities that help providers meet evidence based guidelines. The health systems see the tools and processes they will adopt as Clinical Decision Support (CDS) and sometimes will refer to it as Population Health. CDS not only equips physicians with actionable guidance at the point of care but also helps life sciences translate research into practice, improve adoption of new therapies, and demonstrate real-world value. Life sciences companies often label these types of capabilities as Implementation Science initiatives, Digital Target Product Profile Solutions, or Care Gap Dashboards. For the purpose of this playbook we will refer to these projects under the term CDS.

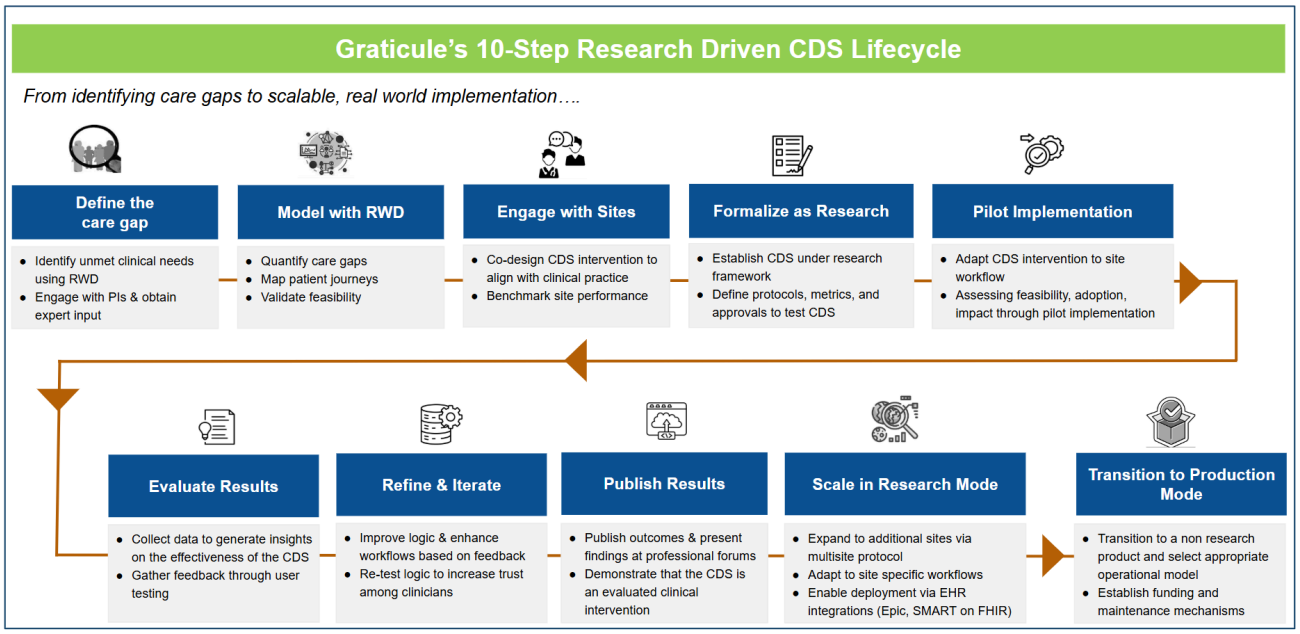
How to scale CDS is a real concern for making investments into working software and processes. After developing a CDS solution at an initial site, scaling it across multiple health systems presents its own set challenges. Each health system requires its own contracts, approvals, and customized implementations, making progress slow, fragmented, and costly. CDS solutions risk becoming trapped in “pilot mode” and never achieving broad adoption outside of the first implementation site.

Graticule brings expertise and strategies, treating CDS initiatives as implementation science, following a structured, research-driven process designed to demonstrate impact, navigate operational complexity, and enable solutions that can scale.



Graticule's Differentiated Research First Approach

We frame the CDS development as a research initiative, often aligned with quality improvement (QI) Research objectives. This allows us to evaluate interventions, generate evidence of impact, and navigate approvals in a structured, research-driven way rather than as a commercial IT project. Our approach spans the full lifecycle of CDS design, development, deployment, and scale-up: from modeling with real-world data to embedding interventions into health system workflows, validating outcomes, and scaling across networks.



Grounded in research-first principles, here is the approach we follow:

Step 1: Define the care gap

We begin by identifying and engaging with PIs and clinical experts to identify care gaps with a high population-level impact, ensuring the project is anchored in a real unmet need. To reduce the burden on health systems and to make a strong business case upfront, we start with analysis of RWD data sources (either through our aggregate data partners or through open source RWD datasets). This allows us to quantify the magnitude of the care gap.

By combining these data-driven insights with input from sponsor clinical teams, PIs, and literature reviews, we establish the clinical relevance and the potential impact of addressing the gap.

Step 2: Model care gaps with licensed real-world data

The purpose of this step is to validate that the approach is feasible and clinically meaningful. Before initiating CDS development at a first site, we license real-world data (RWD) through our data partners or aggregated data sources to gain access to structured (e.g., EMR fields) and unstructured (e.g., notes, imaging reports) data. We leverage the licensed RWD data to map the patient journey, understand the landscape where patients fall through the cracks: missed screenings or missed diagnosis, treatment delays etc. We work with our in-house clinical experts and sponsor clinical teams, to design the CDS intervention. Using the de-identified RWD data, we build a proof-of-concept (POC)/preliminary algorithm and care gap improvement presentation approach that can later be applied to health system data, while reducing the initial burden on sites.

Step 3: Engage with health systems

Step 3a: Engage with PIs/ clinical leaders to translate the POC into health system

Armed with data-driven insights, we connect with sites within Graticule's health system research network or those with which sponsors already have established relationships. We engage with interested PIs or clinical leaders involved in other quality improvement (QI) initiatives, gathering their perspectives on the care gap, understanding site specific workflow challenges and discussing which solutions would be most feasible and effective in their context. We also determine where in the workflow the intervention should be deployed (e.g., pre-visit, during order entry, or at the pharmacy) and which resource type would be most effective to act on the CDS prompts (e.g., physicians, pharmacist or coordinators). This creates alignment and ensures the solution addresses site specific pain points.

Step 3b: Demonstrate value at the site level

We generate site or region-specific estimates of the care gap, using our partner platforms or by collaborating with the site's informatics team to run analytics specific to their local population. We benchmark site performance against guidelines to highlight how care is being delivered at the provider or health system level vs. the desired adherence to guidelines. We then model the opportunity volume that could be unlocked through effective CDS implementation. By providing tailored, site-specific analysis outputs, we enable PIs to act as local champions and position them as internal advocates for change.

Step 4: Formalize CDS as research

To move forward with site level CDS development and deployment, we initiate the development of CDS under a research protocol. We draft research protocol, endpoints, and success metrics that measure clinical and operational impact. We manage the drafting and submission of compliance documentation to ensure regulatory alignment, including IRB/ethics approvals, data privacy safeguards, and security protocols. This may also include working through committees at the site such as the CDS committee or Order Set Committee such that the changes to be implemented have been reviewed and meet sufficient priority to be put into the production build schedule for improvements or QI research projects to be conducted through the EHR.

Graticule serves as the CRO, managing contracting, IRB submissions, technology deployment, and evaluation, while the site participates as a research partner. Sponsor funding covers IT support, staffing, and evaluation, ensuring the health system can engage without bearing the burden of financial investment into the CDS tools and data activities. Framing the work as research enables us to test different algorithms, staffing and workflow models to determine what is effective and practical. For example, pharmacists may be resourced to act on CDS insights, allowing providers to benefit without being overloaded. The costs for using the time for pharmacists for this task can become a part of the overall ROI model but become funded on a research basis to help establish their relative utility.

Step 5: Pilot implementation

We begin with a pilot to test feasibility on a small scale with the interventions built as extensions to the EHR. These pilots allow us to answer foundational questions: Does the intervention work in practice? Where do barriers emerge in workflows, adoption, or patient engagement? For this we work closely with principal investigators (PIs), clinical leaders, and frontline providers inside health systems to understand when and where a CDS would be most useful. We customize the POC/ preliminary algorithm as per site workflow, designing the intervention in a way that it is easier for clinicians to adopt and doesn't impact the existing workflow. We may also build only components and not the full implementation so that we are able to demonstrate that we can achieve the desired value.

Step 6: Run a broad initial test and evaluate results

Through a broader implementation with an experimental design we can establish that the CDS is viable and can be trusted by health systems. This research may be either described in the original protocol for the CDS research, added as an amendment, or established through a new protocol. We use the CDS and collect data to generate initial outcomes and insights on the effectiveness of the CDS. This may occur at more than one health system or may be focused on a single initial health system.

The test is run in a fixed period of time and includes a well designed control such as a subpopulation or set of clinics/physicians not receiving the CDS in order to establish the impact. The scale to select for the study depends on the strategy by the sponsor given that a larger test will likely have a bigger impact on resolving care gaps, provide greater credibility to the tool, but it also will require a higher investment to support many sites and risk negative results due to not having worked through unanticipated challenges.

During the evaluation of the use of the tool the findings are reviewed by clinical experts to confirm that the CDS identifies the right patients and delivers outputs that are clinically relevant and actionable. Additionally we gather feedback through user testing with frontline users such as clinicians, pharmacists, and care coordinators to ensure the intervention is relevant to them and integrates into their daily practice.

Step 7: Refine and iterate

Based on feedback received during pilot implementation, we refine the CDS logic, adjust workflows, and re-test to confirm improvements. This iterative process increases trust among clinicians and strengthens the case for broader adoption. It also may result in adding more sites to establish or implement additional extensibility of the systems to adapt to different health systems, populations, or geographies. This additional research can extend the original research evaluation including addressing the lessons learned from a first phase such that the research is progressive in how results are generated to show the improvement from iterations.

Step 8: Share results and evidence

Once refined, results are presented to the broader community of PIs and clinical teams, shared through peer-reviewed publications and professional forums. This creates external validation and credibility, demonstrating that the CDS is not just a technical tool but an evaluated clinical intervention.

Evidence of impact, both clinical and operational, become the foundation for expanding to new sites either for additional research or as a CDS product with established value to clinicians.

Step 9: Scale across sites in research mode

The next research step is testing scaling in research mode. We identify additional sites where the CDS intervention can be deployed by leveraging established relationships and technology. To streamline expansion, we use a multi-site protocol with centralized IRB approval throughout the project. In our experience working with U.S. health systems, centralized IRBs expedite ethics review. While we still provide site-specific

information to each site's ethics review group, having IRB approval allows most sites to move forward within weeks rather than months, often with minimal or no additional review. Each new site adapts the workflow to its own context while building on a shared research framework, ensuring local relevance and consistency across the network. This balance of rigor and flexibility is what enables CDS to scale reliably across health systems.

By maintaining the project as a research project during the scale phase we also continue to be in a position to provide the health system partners adequate funding and evaluation resources to work through governance processes and establish the implementation of the CDS frameworks. To accelerate adoption, we also work with EHR vendors such as Epic to list our CDS tools into App store type systems such as the Epic showroom, creating visibility and enabling easier replication across additional health systems. We also establish automated deployment systems either to push updates into the EHR configuration or by maintaining cloud based utilities such as SMART on FHIR applications that operate through triggers such as CDS Hooks.

As new improvements are introduced the performance of the CDS and utility is measured in conjunction with participating health systems.

Step 10: Transition from research into production mode

Once significant and compelling research has been published that establishes the utility of the CDS in production use then it can be in a position for transition to a non-research product. We do not see a benefit to rushing to transition to a production support capability. Transitioning while still trying to establish the value and solving for sustainability can limit both the ability to support healthcare institutions who can't establish an immediate ROI for integration of an early stage tool or funded analytics on effectiveness for clinical or site cost savings benefit.

Once it has been established that the CDS can be viable outside of research then we select and work toward a variety of models to establish it as a sustainable solution. These could include some of the following options:

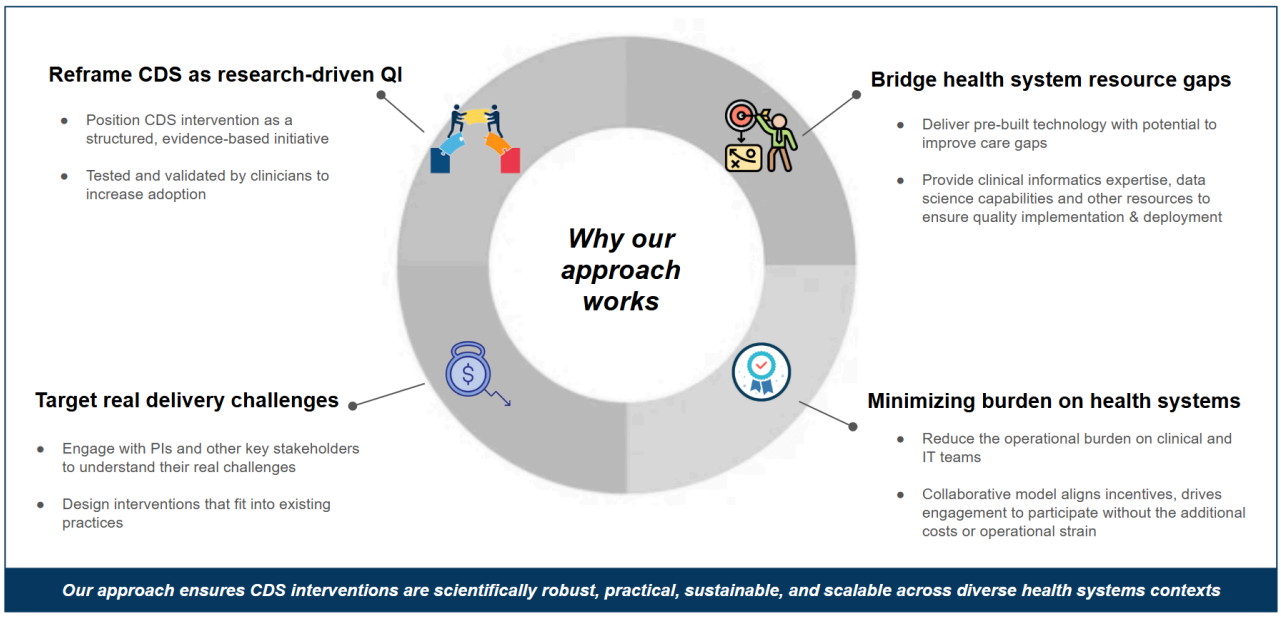
- Transitioning the CDS utility to a patient advocacy group that then offers the capability back to health systems at a cost effective price or as a trusted free utility.
- Making the CDS service available to health systems as a license from Graticule or a Graticule partner based on the economic and clinical value that it provides.

- Moving the CDS tool through a regulatory process such as the FDA SaMD (Software as a Medical Device) approval process to qualify the CDS for use and possibly reimbursement as a device.
- Collaborate with the EHR vendor(s) to incorporate the capability in their base build or optional modules such that the logic and workflows appear in updates embedded in the EHR vendor's upgrade cycles.
- Establish financial mechanisms to establish offerings such that the sponsor can offer the solution to the health system at fair market value. The pricing to health systems may work include connectivity to other contracting such as rebates.

A plan and contracting is needed to establish ongoing funding for maintaining and improving the tool, adoption, and support for sites and partners using it.

Why Our Approach Works

Graticule's approach works because it addresses key barriers that often prevent CDS from achieving meaningful impact.



- **Reframing CDS as research-driven quality improvement**: Instead of treating CDS as a commercial IT deployment on day 1, we position it as a structured, evidence-based initiative. This research-first mindset ensures interventions are rigorously tested, clinically validated by health systems, and trusted by clinicians, increasing adoption and long-term sustainability. This matches how health

systems think about CDS internally as a project that requires evaluation, monitoring, and improvement to ensure it adds value vs. distracting from patient care and billing activities.

- **Bridging health system resource gaps:** Developing, deploying, and evaluating custom CDS interventions requires significant time, effort, and funding, challenges that many health systems face. By providing clinical informatics expertise, data science capabilities and structured research frameworks, we fill this gap and reduce the operational burden on clinical and IT teams.

- **Targeting real delivery challenges:** Our methodology focuses on improving adherence to guidelines and closing care gaps by engaging with PIs and other key stakeholders involved in care delivery such as informatics staff, pharmacists, and care coordinators to understand their challenges and workflows. Through this collaboration, we design interventions that fit into existing practices and then implement and validate them, ensuring the CDS solution improves care delivery. We don't just presume there is a simple reason why actions aren't being taken and by working with providers in health systems we can form hypotheses with them regarding both technical and non-technical issues such as workflow and incentives. We can then provide the tools to the systems to test them and provide answers through credible analysis of results.

- **Minimizing burden on health systems:** Projects are funded through sponsors' medical affairs or evidence-generation functions, allowing sites to participate without the additional costs or operational strain that would otherwise make these projects hard to prioritize or staff. This collaborative model aligns incentives, drives engagement, and supports scalable implementation across multiple sites.

By combining these elements, our approach ensures CDS interventions are scientifically robust, practical, sustainable, and scalable across diverse health systems contexts.

What sets Graticule apart

What makes us distinct is our ability to combine evidence generation, real-world data, and clinical partnerships

- Evidence generation- Expertise in developing protocols, endpoints, and evaluation frameworks that meet both regulatory and scientific standards

- Deep RWD capability- Experience in leveraging RWD data to benchmark performance, uncover care gaps, and model interventions before they are deployed
- Clinical partnerships- Collaborating directly with PIs and health system leaders to design interventions that align with workflows and clinician needs

And importantly, when it comes to scale, Graticule is not starting from scratch. We already work with established research networks/ partners:

- Established network of sites - Graticule works in multiple capacities with sites including RWE, clinical trial optimization, and CDS. We offer tools such as CLEHR and Patient Finder at no cost to sites. Our site network is already at a sufficient critical mass with contracting and technology that enables implementation of CDS research projects.
- EHR vendors (e.g., Epic, Cerner, Modernizing Medicine, Point Click Care) to integrate CDS into point-of-care systems
- Pharmacy networks like LoopBack Analytics, which operate large-scale coordination and patient engagement platforms
- Vendor Services Partnership with Epic, giving us the ability to rapidly deploy existing solutions or design, build, and launch new applications at scale

By building on these trusted networks, we reduce the need for new trust agreements, BAAs, or duplicative operational relationships. This creates a cost-effective and scalable path to deploying CDS across multiple health systems moving from isolated pilots to broad adoption. In short, Graticule bridges the gap between research and delivery, generating evidence that CDS tools improve care quality, while embedding them into scalable, real-world workflows.

Interested in learning more?
Reach out to us at info@graticule.life

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