RegenMed

WHITE PAPER

ACCELERATING DEMAND FOR VALIDATED REAL-WORLD EVIDENCE

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RegenMed

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General

Real-World Evidence has rapidly transitioned from a secondary data stream to a core strategic asset for both regulators and industry. The FDA's evolving frameworks and successful precedent cases have validated RWE as an acceptable basis for regulatory decision-making. Meanwhile, private sector stakeholders are embracing RWE for market access, commercialization, and innovation. As data infrastructure, methods, and regulatory guidance continue to mature, RWE will increasingly shape the future of evidence-based medicine.

The FDA defines RWE as "the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD)," which includes data from electronic health records (EHRs), claims and billing activities, product and disease registries, and patient-generated data including from mobile devices. [1]

The 21st Century Cures Act (2016) formally directed the FDA to expand its use of RWE to support new indications for approved drugs, post-approval requirements and monitoring, and device approvals under the least burdensome provisions. This legislation marked a regulatory turning point by mandating the integration of RWE into the agency's evidence hierarchy. [2]

The FDA's 2018 *RWE Framework* outlines how the agency evaluates whether (i) RWD is "fit for use", (ii) the trial design is adequate, and (iii) the analysis meets regulatory standards. Since then, the FDA has issued multiple guidance documents to formalize RWE's use in regulatory submissions, including guidance on data reliability, external controls, and non-interventional studies. [3]

Illustrative Use Cases

RWE has already played a pivotal role in several FDA approvals:

- **Ibrance (palbociclib):** Expanded indication supported by RWD from Flatiron Health.
- **Label expansion for Tecentriq (atezolizumab):** Supported by RWD from EHRs.
- **Medtronic's CRT-D device:** Approved based on real-world registry data rather than an RCT.

These cases underscore the FDA's growing willingness to accept high-quality RWE as valid regulatory evidence, especially when randomized controlled trials (RCTs) are infeasible. [4]

WHAT IS REAL-WORLD EVIDENCE

Biopharmaceutical companies are now embedding RWE across the entire product lifecycle:

- **Drug Development:** Using RWE to inform trial design, select endpoints, and simulate control arms.
- **Market Access:** Supporting payer negotiations and health technology assessments (HTAs).
- **Post-Market Surveillance:** Monitoring safety and effectiveness under real-world conditions.

A 2023 Deloitte survey found that 92% of life sciences companies had RWE strategies in place, and 68% planned to increase investment in RWE infrastructure. [5] Payers also are increasingly using RWE to evaluate treatment value, manage formularies, and negotiate value-based contracts.

For instance:

- UnitedHealthcare and Aetna both use RWE to adjust reimbursements based on real-world outcomes.
- ICER (Institute for Clinical and Economic Review) frequently incorporates RWE in its assessments.

This signals a paradigm shift: therapies are judged not just by RCT efficacy, but by how they perform in broader, more heterogeneous patient populations. [6]

THE DEMAND FOR PRIMARY, VALIDATED REAL-WORLD DATA

Summary

Real-world data collected directly from physicians and patients with specific research questions in mind provides superior clinical richness, adaptability, and validity compared to passively harvested EMR or claims datasets. While retrospective data sources are useful for hypothesis generation and surveillance, regulatory-grade and practice-changing insights require the rigor, context, and control only achievable through purposeful, prospective RWD collection.

THE DEMAND FOR PRIMARY, VALIDATED REAL-WORLD DATA

Fit-for-Purpose Data Quality

Data collected prospectively from physicians and patients specifically tailored to a research question is inherently more fit-for-purpose than retrospectively extracted data not originally designed for research use. EMR and claims data are collected primarily for billing and documentation, not for answering scientific or clinical questions. This often results in missing variables, misclassified diagnoses, and inconsistent data structures.

In contrast, prospectively collected data enables the use of validated instruments, structured formats, and clinically relevant endpoints from the outset.

"Data collected in the course of routine clinical care may not contain the variables needed to answer a particular research question or may contain them in a non-standardized or incomplete format."
(FDA RWE Framework (2018), p. 8)

Clinical Context and Nuance

Physician-entered data in the context of a registry or structured real-world study can capture clinical rationale, nuance, and narrative details that are often absent in EMRs and claims. EMRs are often plagued by "note bloat" and copy-paste practices, obscuring critical insights or creating data noise.

In contrast, structured physician reporting tied to research goals allows for the capture of disease staging, physician assessments of severity, treatment intent, and other decision-making context.

"Clinician involvement in data collection enables the integration of medical judgment and ensures relevance to patient outcomes." *(Registries for Evaluating Patient Outcomes: A User's Guide, 4th Ed., AHRQ (2024), Ch. 3)*

Patient-Reported Outcomes and Longitudinal Engagement

Direct data collection enables inclusion of patient-reported outcomes and active follow-up, which are often absent or unreliable in EMR or claims-based data. The former directly engages patients for metrics like pain scores, functional capacity, mental health, quality of life, and treatment satisfaction. Retrospective datasets rarely include this, or rely on proxies like medication use, which do not fully reflect patient experience.

"Including the patient perspective is critical to understanding treatment effects in real-world settings… registries are well suited to collect these data."*(AHRQ User's Guide, 4th Ed., Ch. 4.)*

THE DEMAND FOR PRIMARY, VALIDATED REAL-WORLD DATA

Timeliness and Scientific Agility

Direct collection allows researchers to design agile, rapid-learning systems and capture emergent phenomena as they arise, rather than waiting for retrospective datasets to mature. Retrospective EMR and claims datasets often lag by 6–24 months, making them less responsive to evolving clinical landscapes (e.g., COVID-19, novel therapies).

Prospective physician-patient data collection can be adapted in real time, such as adding new fields when clinical practices change or new safety signals emerge.
"Registries can be modified mid-course to include new endpoints, populations, or risk factors, unlike static datasets." (*FDA RWE Framework* (2018), p. 13)

Data Integrity and Source Verification

With prospective collection, especially via digital tools integrated at the point of care, data provenance is clear, and validation can occur at entry — unlike EMRs and claims, which require extensive and error-prone *post hoc* cleaning.

Also, EMR fields are often unstructured, and key fields like medication adherence, dosage, or lab results may be missing, miscoded, or duplicated. A purpose-built collection platform with structured eCRFs, logic checks, and integrated clinical decision support ensures data reliability and traceability.
"Manual data abstraction from EMRs is time-consuming, error-prone, and often lacks key clinical detail." (*Harvard Catalyst, RWD Challenges Report* (2022))

Scientific Validity and Credibility with Regulators and Payers

Purpose-collected RWD is increasingly preferred for regulatory-grade evidence when high internal validity is needed, such as for label expansions, health technology assessments (HTAs), or comparative effectiveness studies.

While regulators like the FDA are open to RWE from EMRs and claims, they emphasize data relevancy, reliability, and transparency, all of which are stronger in well-designed prospective datasets.
"Not all RWD is created equal… data should be collected and curated for the research question to ensure scientific validity." (*FDA Real-World Evidence Guidance* (2021), Section III.)

Each Circle [7] represents a well correlated, high-quality and statistically significant dataset. Each is specific to a single anatomical region, pathology, treatment protocol, and standardized outcome assessment. Data is derived directly by physicians in the context of their everyday delivery of clinical care. (As discussed in our separate White Paper, it is therefore not generally subject to IRB review.)

Circles datasets are thus analogous to "big data" real-world evidence real-world data sources, [8] but with following significant advantages:

- Superior clinical context and relevance.
- Data specifically relating to impactful clinical/scientific questions, as opposed to CPT, ICD, prescription or other codes.
- Complete flexibility in designing Observational Protocols (OPs) from the ground up. This allows the capture of particular products, product settings, adjuvant and adjunct therapies, social determinants of health, remote patient device inputs, etc.
- Automatic correlation of long-term standardized outcome assessments to specific clinical/scientific questions.
- Fully de-identified for purposes of HIPAA and GDPR.
- All foundational data can be fully validated to primary sources in terms of author, time of entry, and editing.
- All datasets are unambiguously owned by contributing physicians and Regen Med. Contributing physicians share in monetization from such datasets, resulting in strong motivation to contribute applicable real world data.
- Circles datasets constantly grow in clinical significance, due to the continual addition of Cases by participating physicians as well as the accumulation of longer-term patient reported outcomes.

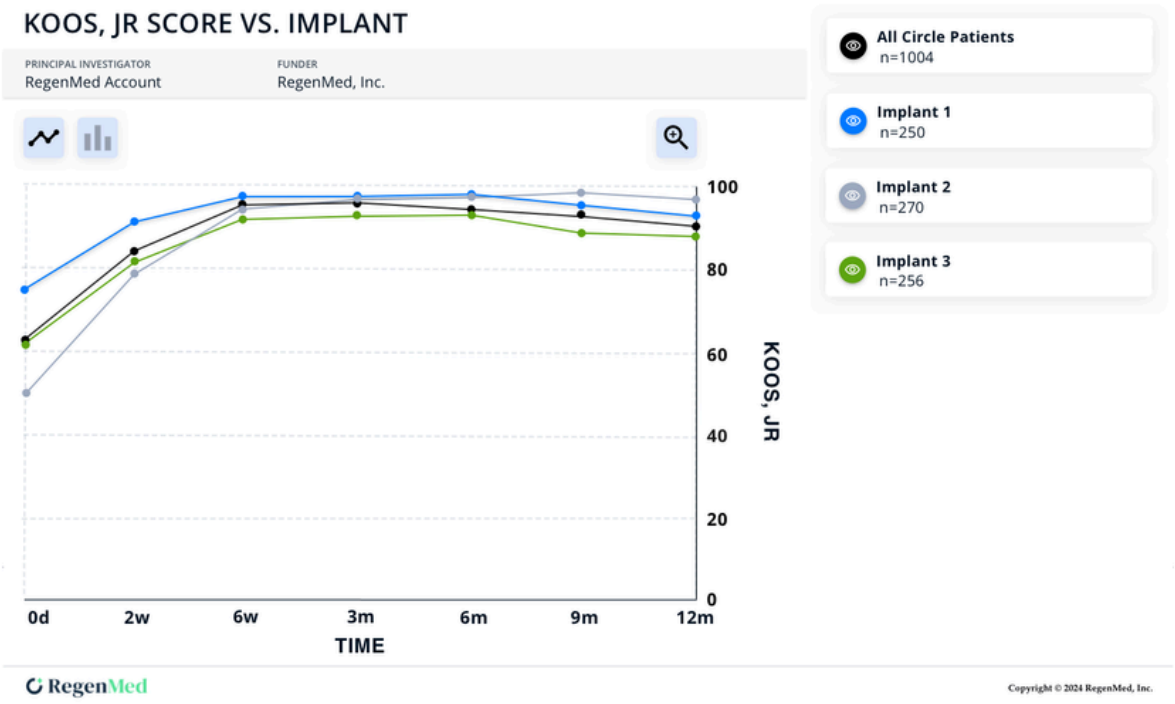
Illustrative Circles Reports

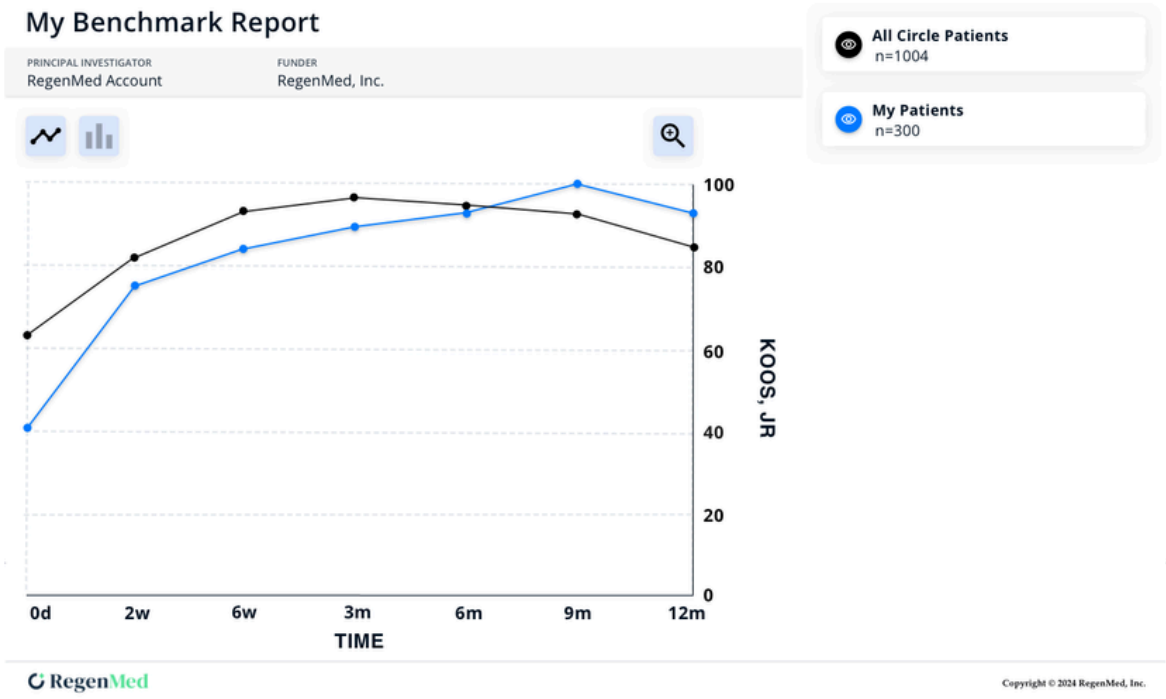
Because of the *a priori* flexibility in designing OPs, as well as the large number of internally correlated Cases, Circles datasets will yield a number of valuable correlations. Illustrative reports for current versions of the TKA and THA Observational Protocols are provided in the Appendix.

On the one hand, these reports indicate the deep, granular and verifiable correlations which are accessible to licensees of Circles datasets. On the other hand, the generation of such datasets does not by itself require IRB approval except as and when decided by Circles sponsor. This is because Circles datasets comprise HIPAA-compliant real-world clinical data collected during the course of regular medical care to evaluate and improve established treatment protocols — without introducing novel interventions or intending to produce generalizable scientific knowledge.

APPENDIX: ILLUSTRATIVE TKA AND THA CIRCLES REPORTS

TKA





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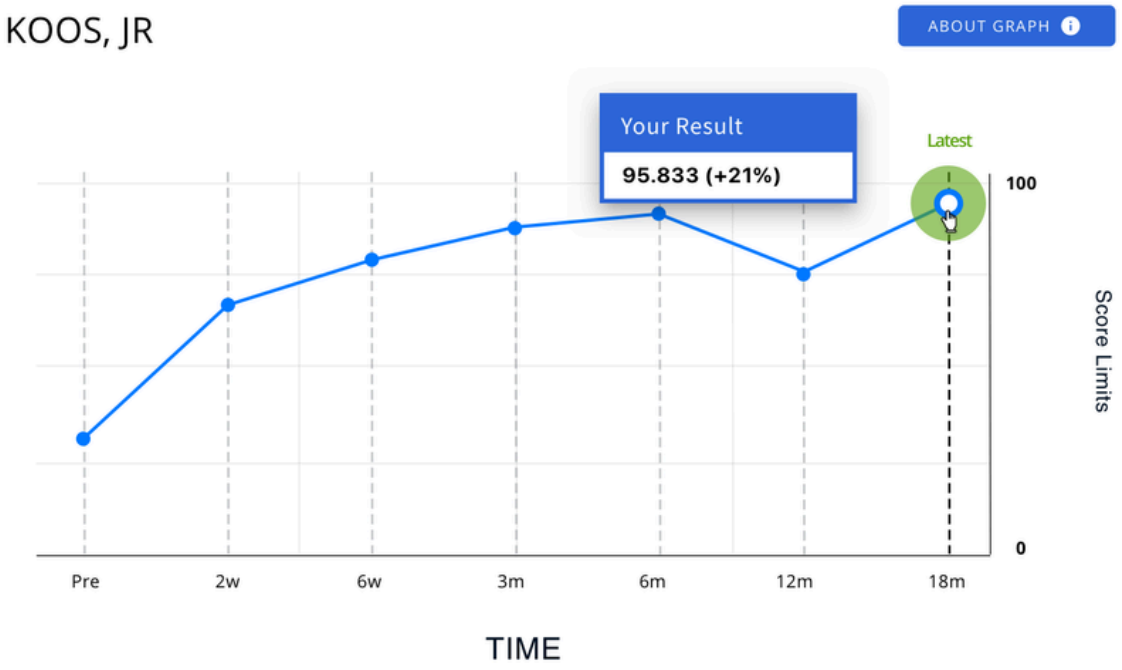
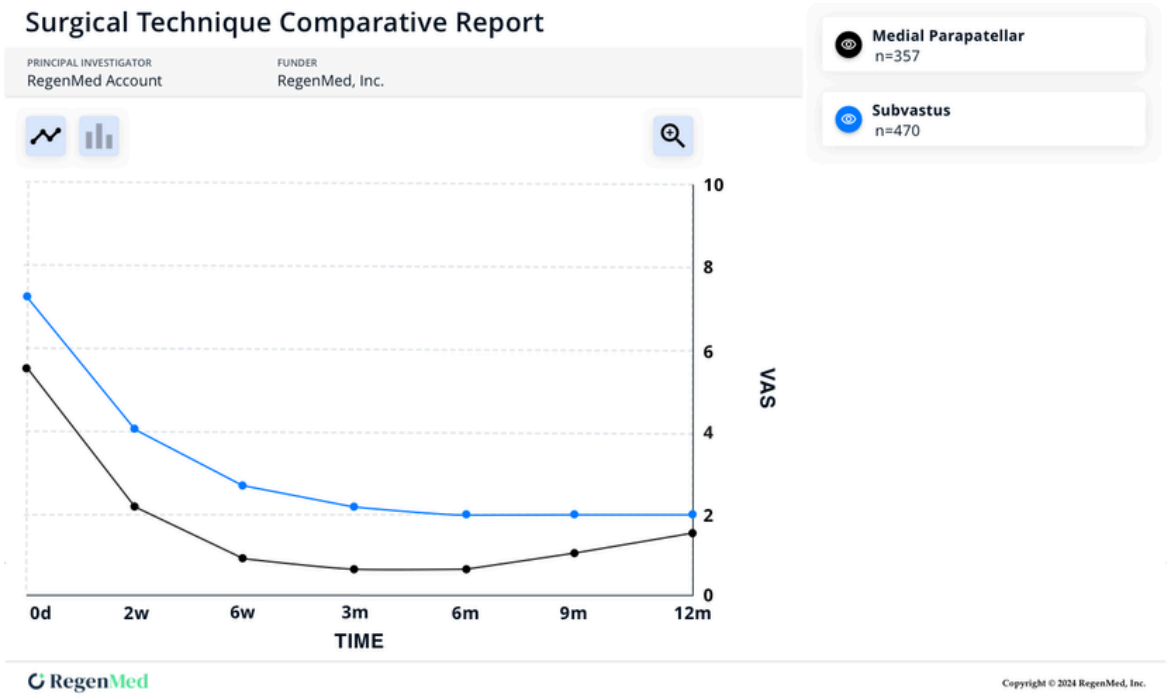
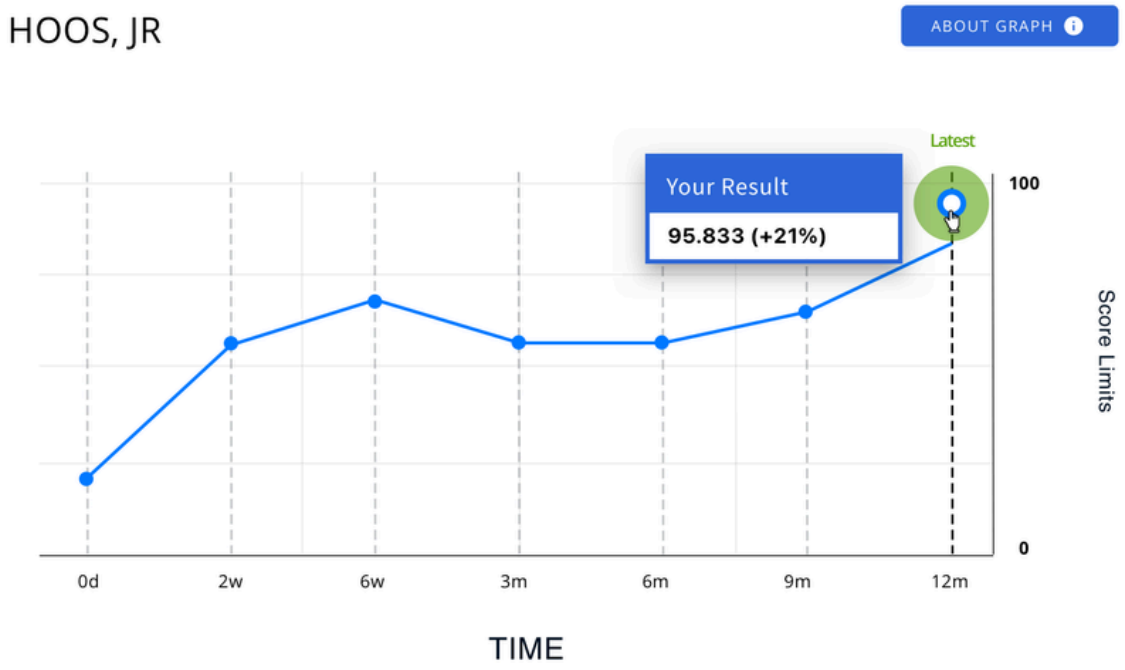
TKA

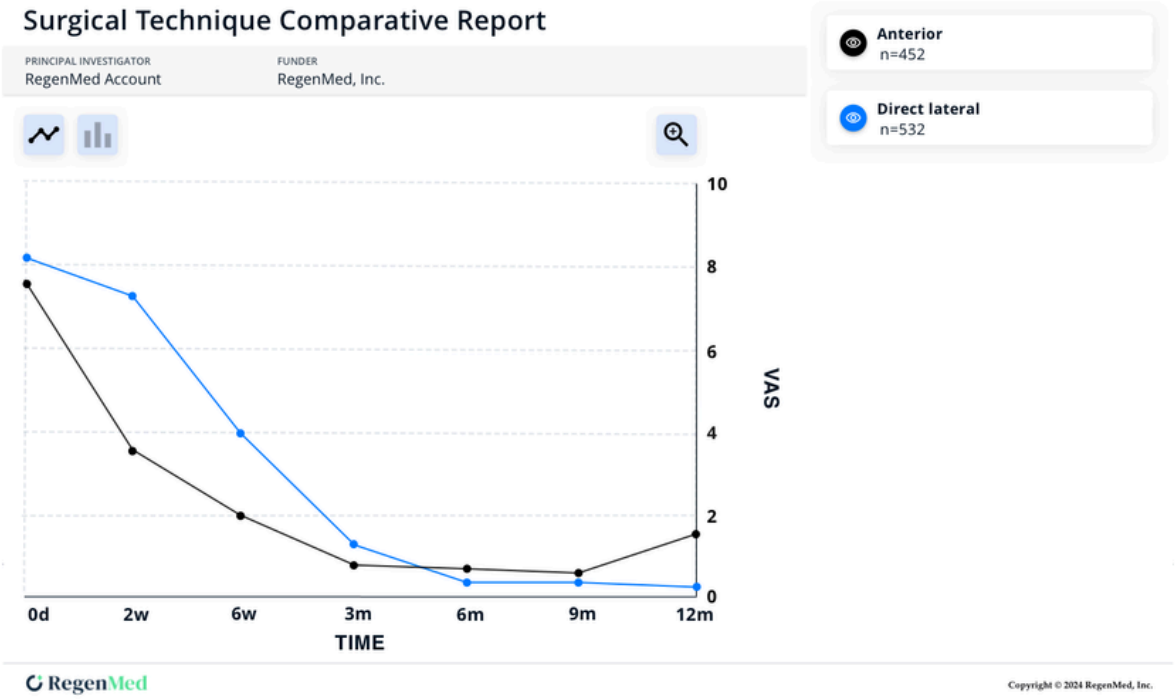




APPENDIX: ILLUSTRATIVE TKA AND THA CIRCLES REPORTS

THA





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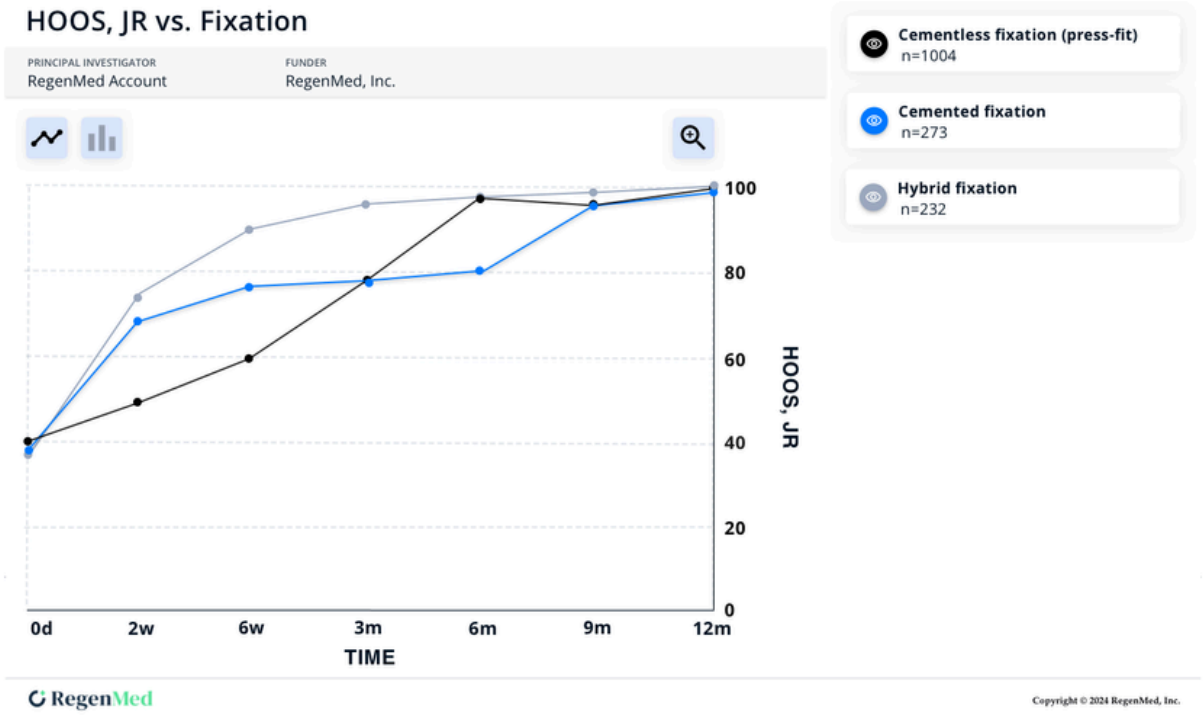
THA



FOOTNOTES

1. FDA (2018). *Framework for FDA's Real-World Evidence Program*. https://www.fda.gov/media/120060/download. See also AHRQ's Registries for Evaluating Patient Outcomes: A User's Guide, 4th Edition.
2. *21st Century Cures Act*, Section 3022. U.S. Congress, 2016. https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf
3. FDA (2021). *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making*. https://www.fda.gov/media/152503/download
4. FDA. *RWE Case Studies and Examples*. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
5. https://www.deloitte.com/us/en/Industries/life-sciences-health-care/about.html
6. Deloitte (2023). *Survey of Real-World Evidence Strategy in Life Sciences*. https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/real-world-evidence.html
7. Circles are based on RegenMed's patented Circles technical platform (inCytes™ and Benchmarc™) and associated processes.
8. See for example IQVIA, Duke Health, Komodo Health, Mayo Clinic. For more information, see Advantages of Circles Over Big Data.