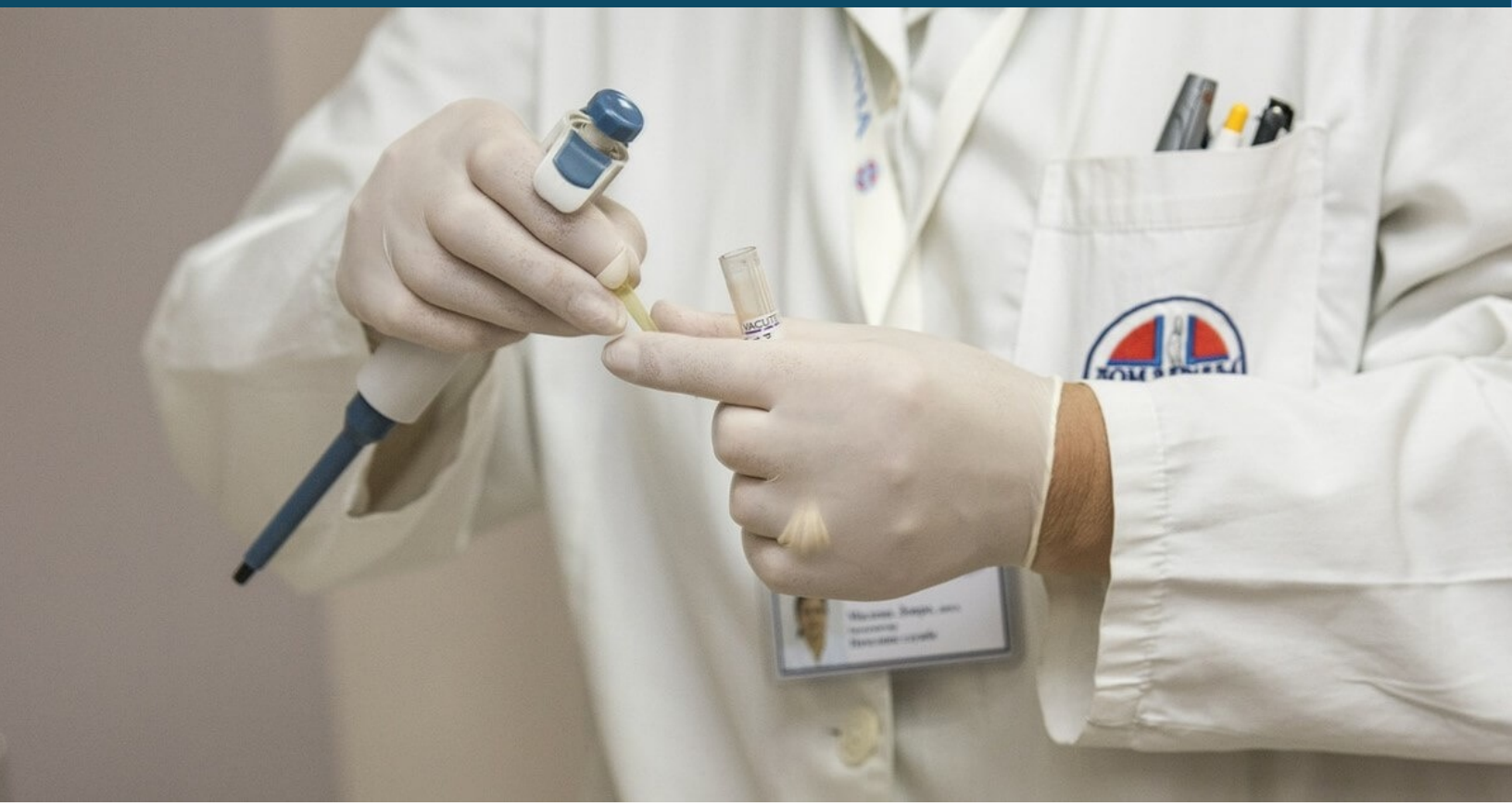
RegenMed

WHITEPAPER

Circles as Off-Label Communications Platforms for Manufacturers and Distributors



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Introduction

Off-label usage and communications represent critical patient care, legal, reputational and monetary considerations. On the one hand, off-label clinical use is legal and common. Off-label prescriptions account for at least 20% of scripts written — more than 100 million instances in the U.S. alone. Indeed, off-label device and medication usage may be higher in certain patient segments and is even considered standard of care for some indications. (See here for example.)

On the other hand, the criminal and civil liability associated with misleading or unsubstantiated off-label marketing is severe. As the F.D.A. has said:

> "...if physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."

The Federal False Claims Act and state counterparts provide strong incentives to whistleblowers and prosecutors to pursue claims against manufacturers and distributors. A list of various settlements, which of course does not include legal fees and reputational damage, can be found here. This liability can apply to healthcare professionals as well. Therefore, direct-to-physician marketing can backfire — HCPs will not want to use a product where the associated marketing may expose them to liability. Nevertheless, manufacturers and distributors remain under financial pressure to find legitimate ways to justify off-label usage. Regulatory approval for an additional indication requires many millions of dollars and many years.

The most effective solution to the foregoing challenges is a process whereby HCPs can themselves evaluate, in a statistically-significant manner, the safety and efficacy of a specific off-label use. As discussed below, the essence of Circles is facilitating this evaluation.

Circles for Evidence-Based Off-Label Use

General

The most effective communications to healthcare professionals are those coming from their own peers, delivered in their everyday clinical language and which address a relevant professional objective. Every Circle meets each of these criteria.

Circles are, in essence, active and continual HCP collaboratives. They utilize a product-agnostic platform (inCytes™) and clinically-efficient processes to allow HCPs to analyze the issues most important to them in their everyday practices, and benefit from statistically significant correlations addressing those issues. Circle Members communicate with each other in a language they understand, and which they find most impactful — that of real-world data and the real-world evidence those data generate.

Circle Members are not forced to create or join a Circle. Rather, they do so voluntarily to identify and evaluate clinical data relevant to a shared clinical objective. That objective is articulated from the beginning in the form of an Observational Protocol accepted by all Circle Members. This ensures that the real-world data deriving from the Circle is deemed relevant and, in statistically significant amounts, useful.

Thus, Circle Members are speaking with each other about real-world data they trust. And they are speaking in a language — verifiable clinical data — which they have chosen and understand. Finally, Circle Members are highly motivated to engage with each other around the Observational Protocol and corresponding real-world data. They are all seeking to address a shared and well-defined objective.

Circles are thus attractive to clinicians because they enable, in a clinically efficient manner, the generation of real-world evidence which supports practice growth and the achievement of professional aspirations.

Circles for Evidence-Based Off-Label Use

General Continued

A Circle is not a mere PROM, EDC, EMR, patient survey or similar piece of healthcare data software. Rather, a Circle represents:

A continually engaged collaborative of healthcare professionals focused on a specific clinical/scientific Observational Protocol.

supported by

The technical platform needed to integrate real-world data corresponding to that Observational Protocol in a turn-key, low-cost and clinically efficient manner.

which is then

Communicated and promoted in a manner motivating clinicians to participate.

and, finally, which results in

Original, verifiable, integrated and statistically significant real-world datasets capable of yielding multiple correlations with clinical, scientific and/or financial value.

Circles for Evidence-Based Off-Label Use

Implementation

Including a medical device or product into the Circle "conversation" among its members represents a powerful HCP communications opportunity for a manufacturer or distributor. An industry Sponsor's product may be explicitly or implicitly incorporated into the Observational Protocol of a Circle. ***(Appendix A, Figure 11.)***

Any Observational Protocol typically involves several medical products. While the principal objective of a Circle may not be to compare one product against another, Circle Members are generally seeking to develop correlations leading to standardization of clinical interventions. They are thus interested in standardizing the products utilized in the context of aggregated data sets which substantive better, more predictable outcomes ("real-world evidence").

A manufacturer or distributor has access to aggregated data resulting from all Circles which it sponsors. At the same time, it is able to avoid any communications with clinicians which might be construed as promotional or marketing. To the contrary, all communications would be – exclusively if desired by the Sponsor — by and among the clinical Circle Members themselves. Moreover, those communications will concern what is of most interest to and valuable for the Sponsor — how its product can most effectively be used in the context of everyday clinical interventions.

The sequence for using Circles to evaluate and achieve off-label usage would be:

- RegenMed, working with its client and one or two of its existing HCP customers, develops an Observational Protocol and other Circle elements incorporating the relevant product. (RegenMed provides all onboarding, training, support and other services for these initial Circle Founders.)

Circles for Evidence-Based Off-Label Use

Implementation Continued

- Everyday clinical Cases generate longitudinal and aggregated real-world datasets comprising real-world evidence in the context of the specific indication and treatment path reflected in the Circle's Observational Protocol. (A Founder can easily establish any number of Circles to accommodate other indications and treatment paths as well.)

- Through articles, conferences, webinars, podcasts and posts — often supported by RegenMed — these initial Circle Members report on and discuss study design, treatment paths, the product, outcomes and other real-world evidence.

- As a result of this natural "promotion," other HCPs with similar clinical interests seek to join the Circle, request information about the protocol, establish protocol variations and otherwise engage with the Circle and its Founders.

- The original Circle, other Circles utilizing variations of the original Observational Protocol, number of Circle Members and valuable real-world evidence grow exponentially.

By sponsoring Circles, a product distributor and/or manufacturer achieves more than off-label usage evaluation and support. It also develops a growing base of engaged HCP users, data-driven patient education materials, a built-in post-market surveillance platform, and the foundation for handling additional products in the same therapeutic area.

Circles Functionality

The turnkey and integrated platforms and processes underlying Circles are enterprise grade and robust. Select elements include the following. (Corresponding diagrams and screenshots are included in Appendix A.)

- Each Circle Founder manages his/her own Circle. In the event of a third-party Sponsor (such as a manufacturer or distributor), that Sponsor manages the master registry (Circle) into which the results of all such contributing Circles are aggregated. ***(Figure 1.)***

- Each Sponsor-approved Circle determines its membership, protocol, localized privacy settings, including server locations, handling of PHI, roles and permissions for Members, patient consent language, branding and other Circle elements. (***Figure 2.)***

- Circle Members can see Circle data in real-time, 24/7/365 from any device. Members of multiple Circles can see the data from all such Circles. The Sponsor, as a Member of all approved Circles, can see and aggregate the data emanating from all such Circles.

- "Root Protocol" functionality ensures aggregation of consistently formatted data even from user-customized protocol versions. ***(Figure 3.)***

- The inCytes™ platform supporting Circles already contains dozens of standardized PROMS which can be incorporated into any Observational Protocol. In addition, its custom eCRF builder supports flexible question creation, modification, and gamification. It is possible, for example, to correlate data derived from custom questions to those derived from standard assessments. ***(Figures 4 and 5.)***

- The integrated patient portal that supports customized treatment path, outcomes, benchmark, uploaded images, PDF's, and other recording and reporting utilities. It also automates e-consent execution and maintenance and includes robust user verification. ***(Figure 6, 7 and 8.)***

Circles Functionality

Continued

- There are multiple clinician and patient customization features. ***(Figure 9.)***
- Circles efficiently integrate real-world data from scribes, clinical team members, laboratories, call centers, wearable health devices. Messaging formats are FHIR/HL7 compatible. Full data auditability and related functions greatly simplify IRB and medical ethics committee submissions.
- Powerful filtering and other reporting features mean continual generation of multiple correlations leading to well supported real-world evidence with demonstrable value for Circle Members, patients and Sponsors. ***(Figure 10.)***
- Sustained, multi-channel promotion of Circles, driving additional Circle Members, Circles, and Cases, and therefore richer, more statistically significant datasets. ***(Figure 12.)***
- Circles data and other elements are accessible in real-time 24/7/365 from any device, including mobile platforms, anywhere in the world.
- Full-time, dedicated Company teams handle product development, regular releases, quality control, and Levels 1 and 2 customer support.

RegenMed

The Evidence-Based Network

Regen Med's offers the leadership, systems and professionalism required to help materially improve medical product sales revenues and margins by generating and exploiting real-world evidence.

The Company works in most regions around the world, and with large hospital systems as well as individual clinicians and medical scientists. Through Circles, it and its clients are generating – and developing demonstrable value from – real world evidence in a variety of therapeutic areas. See the Company's Latest page for examples.

Visit www.rgnmed.com to learn more.

RegenMed

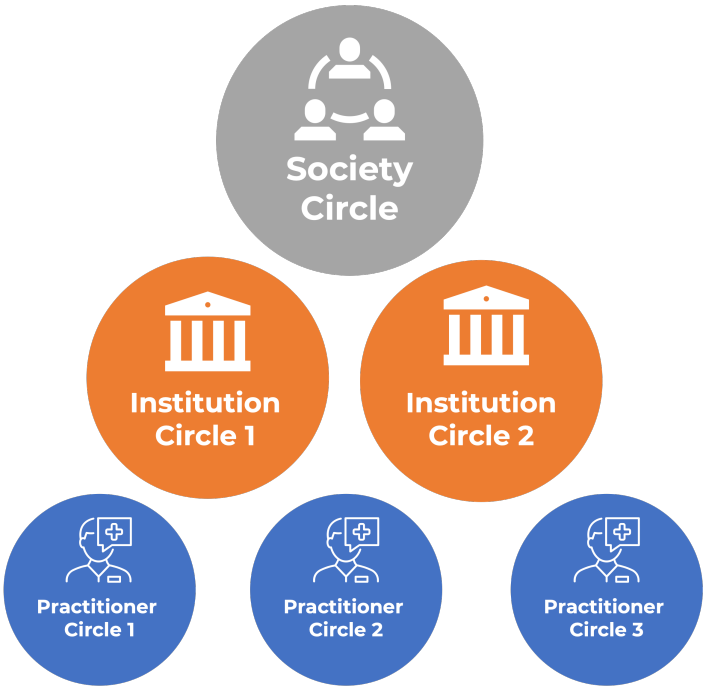
Get Started with Circles

Interested in learning more about RegenMed's Circles? Speak to an expert today.

Contact Us Today

Appendix A Figures

Figure 1



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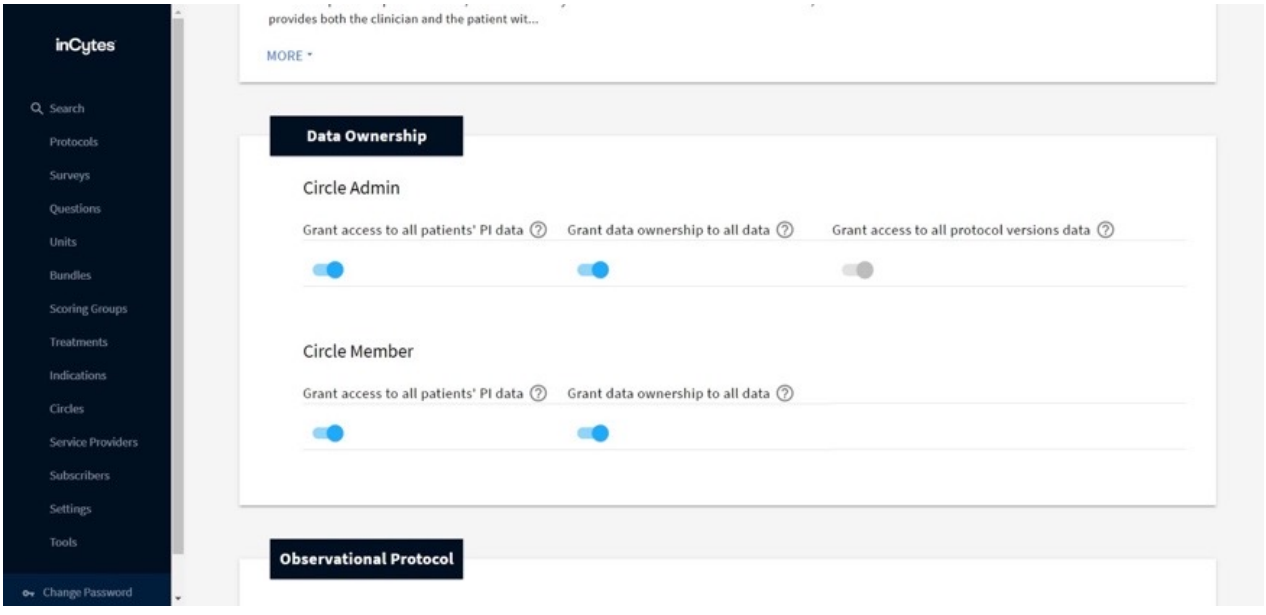

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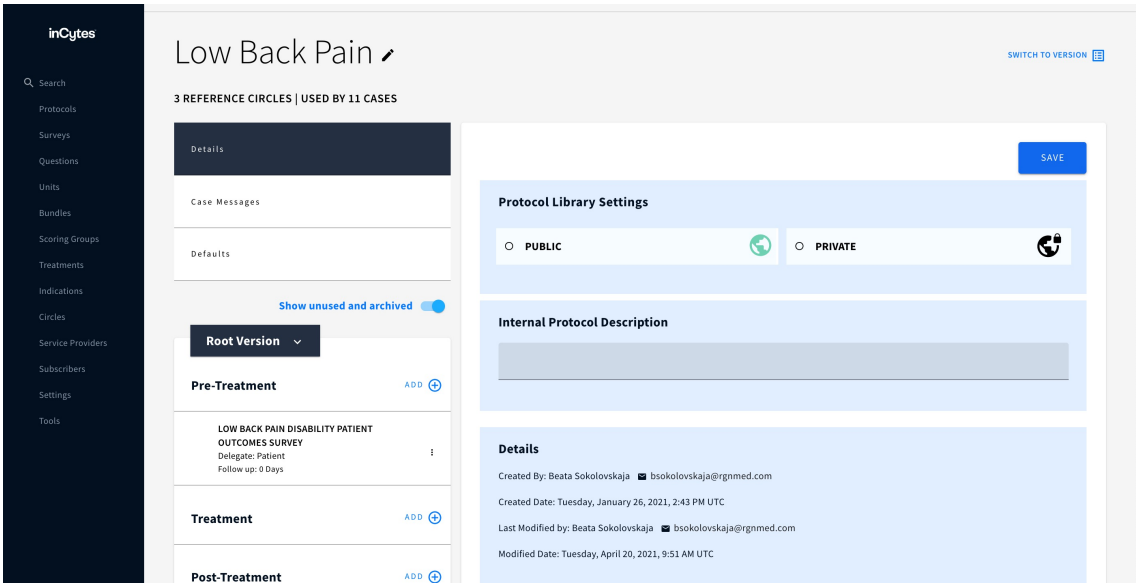
Figure 3



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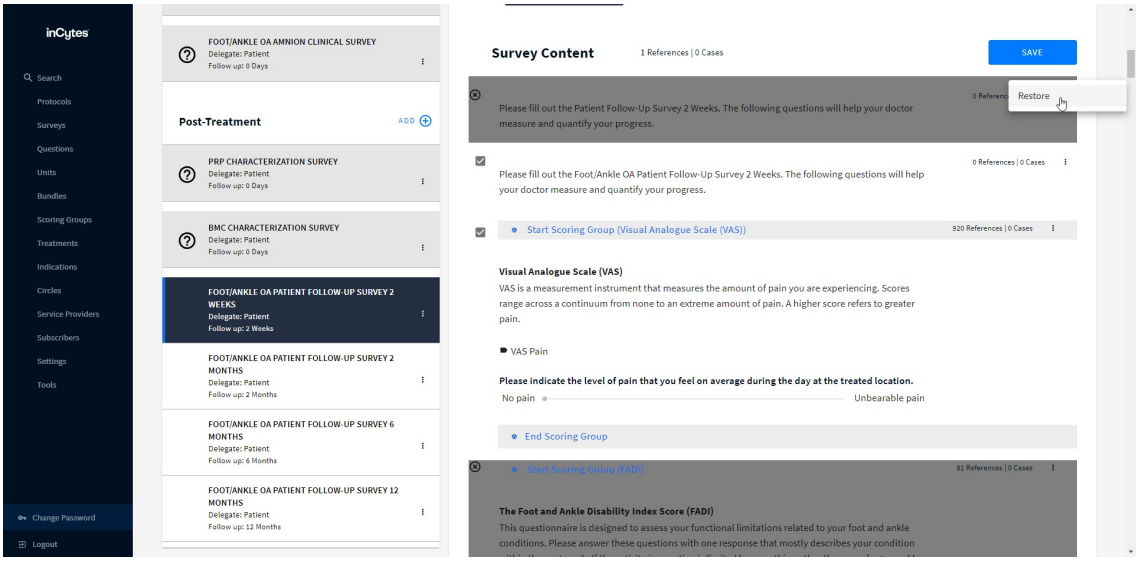

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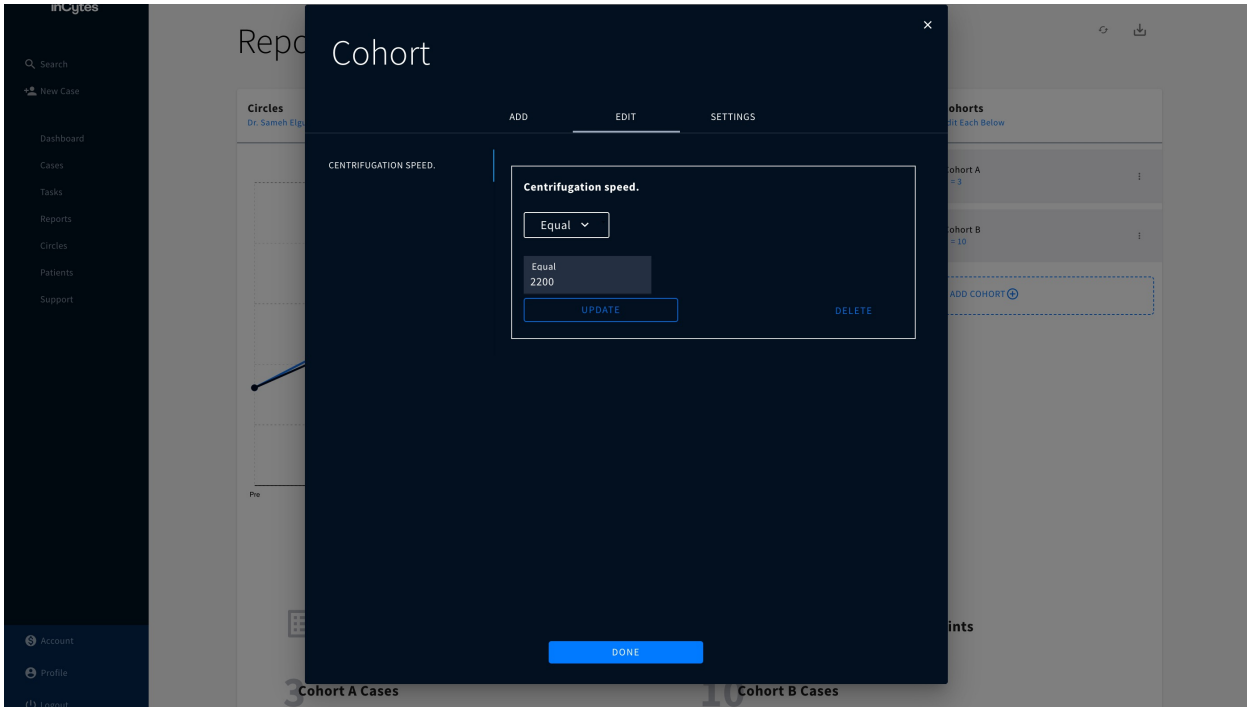
Figure 5



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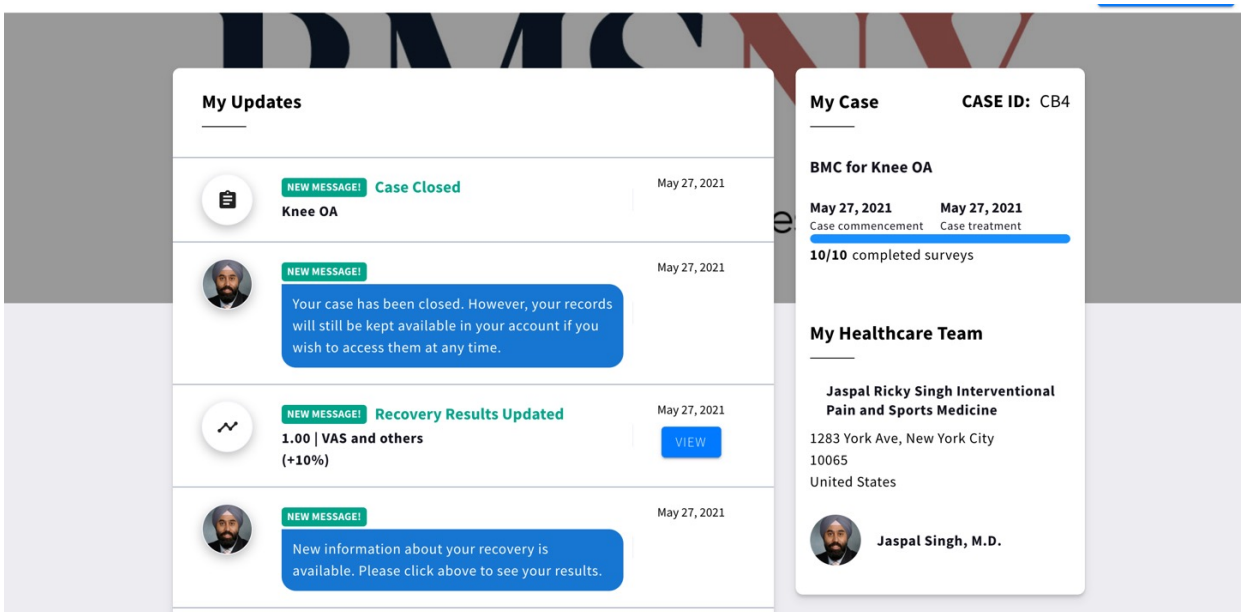

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Figure 7

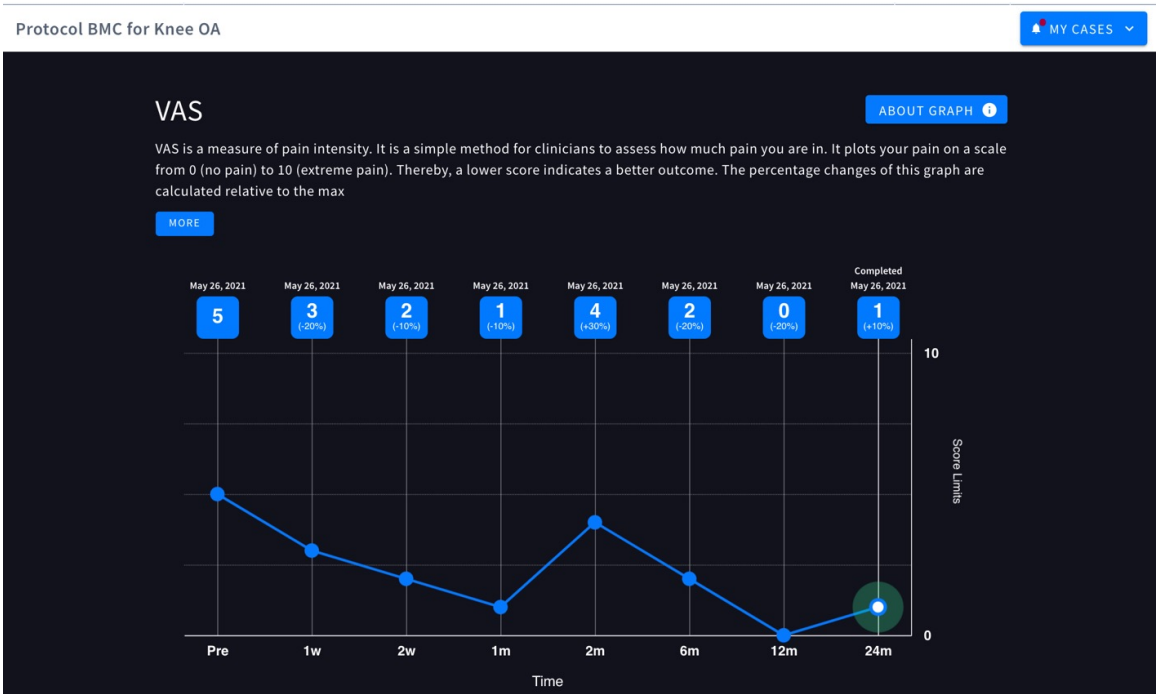

Figure 8

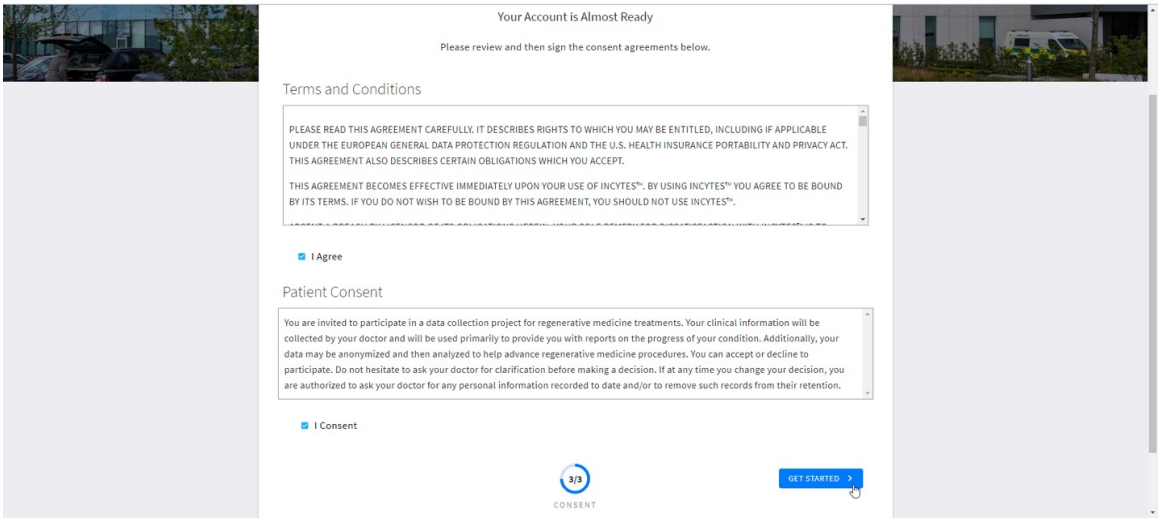

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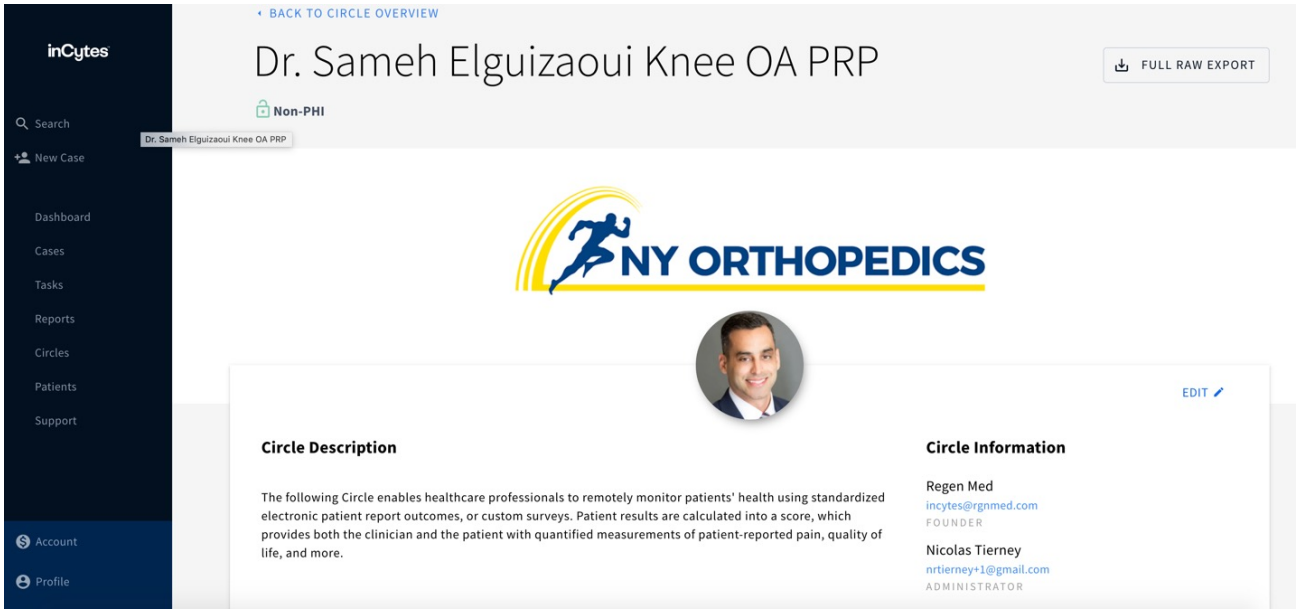
Figure 9



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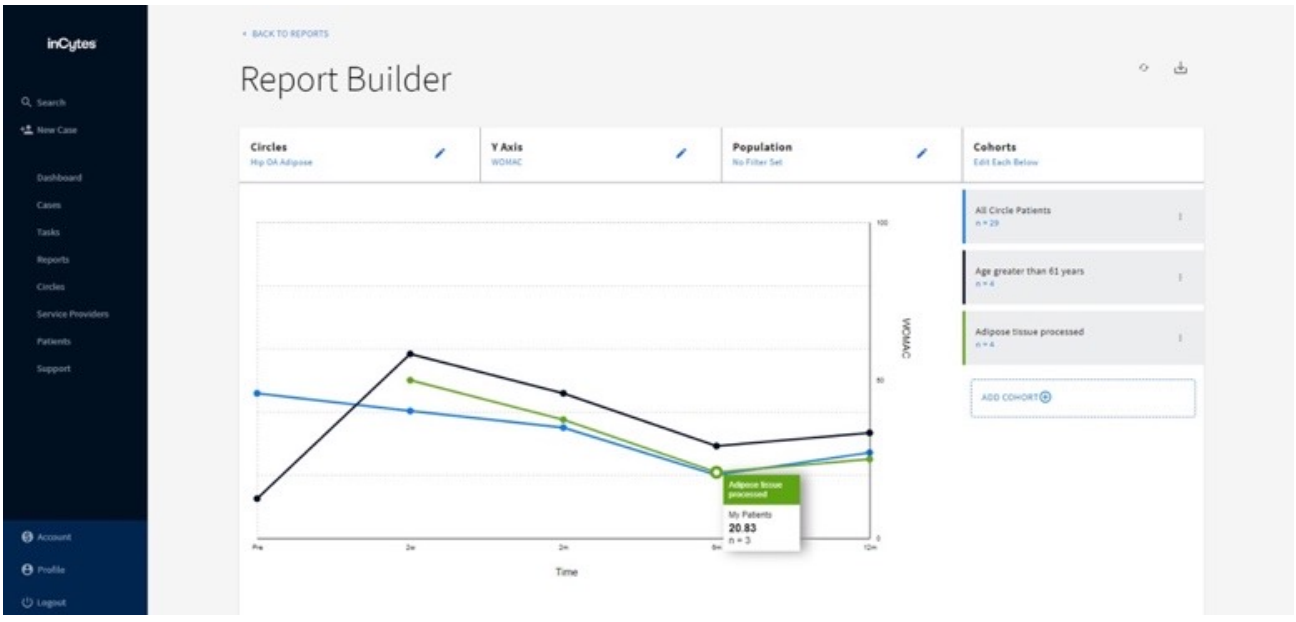

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Figure 11

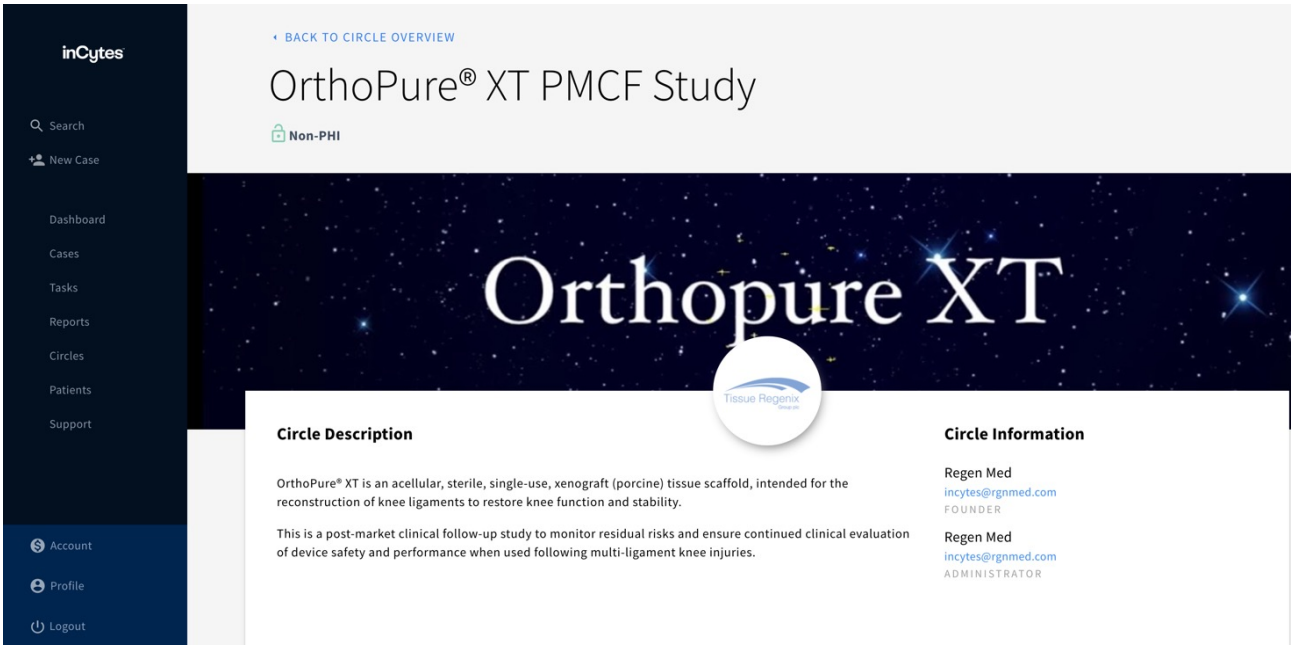

Figure 12