Johns Hopkins University

Journey Through the Federal Loophole; Behavioral Trends Among Physicians Practicing Regenerative Medicine

A Capstone Paper Submitted to the Krieger School of Arts and Sciences Advanced Academic Programs In Partial Fulfillment of the Degree of Master of Science in Research Administration

by

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Abstract

Regenerative medicine therapies have shown potential in treating conditions previously deemed incurable. Though still categorized as investigational by the Food and Drug Administration (FDA), these treatments have gained popularity and are offered at both public and private practices. Platelet Rich Plasma (PRP) and Bone Marrow Aspirate Concentrate (BMAC) regenerative medicine therapies are provided to patients at the Mayo Clinic at multiple departments throughout the institution at different locations. This study characterized the practice, preferences of the practitioners, and perceptions of product efficacy, safety and regulations. Data was collected using a questionnaire focusing on attitudes and behaviors of those performing BMAC and PRP procedures. A total of 8 Mayo Clinic practitioners responded to the questionnaire. The cumulative outcomes of the study provided a baseline understanding of the procedures, how often they are performed, and the indications for which they are most commonly used. Detriments to performing research were also studied and most commonly identified as lack of time and funding. Perceptions of current regulations, reactions to scenarios of possible outcomes of controlled double blind clinical trials and their impact on the practice were also assessed. Results were also used to identify how to best implement new FDA regulations into the practice.
Table of Contents

Abstract ................................................................................................................................. ii

Figures ................................................................................................................................. vi

Tables ................................................................................................................................. vi

Charts ................................................................................................................................. vi

Glossary ............................................................................................................................... vii

Abbreviations ....................................................................................................................... viii

Chapter 1. Introduction ......................................................................................................... 1
  1.1. Background .................................................................................................................. 1
  1.2. Statement of the Problem ......................................................................................... 1
  1.3. Project Questions ..................................................................................................... 3
  1.4. Research Objectives ............................................................................................... 4
  1.5. Significance ............................................................................................................. 4
  1.6. Exclusions and Limitations .................................................................................... 5

Chapter 2. Literature Review ............................................................................................... 6
  2.1. Overview of Literature Review ................................................................................ 6
  2.2. Current practice of stem cell based and regenerative medicine therapies in the United States ........................................................................................................ 6
  2.3. FDA perspectives .................................................................................................... 7
  2.4. Regulations applying to BMAC and PRP products .................................................. 8
  2.5. Regulations Applying to PRP Products ................................................................... 11
  2.6. Disagreements in Interpretation of FDA Regulations ............................................. 11
  2.7. National and International Society Perspectives on Regenerative Stem Cell Therapies .............................................................................................................. 12
    2.6.1. International Society for Cell and Gene Therapy Perspective ......................... 13
    2.6.2. International Society for Stem Cell Research Perspective ............................... 13
    2.6.3. AABB Perspective ............................................................................................ 13
  2.8. RMAT Designation .................................................................................................. 14
Figures

Figure 1. FDA Flowchart for Determining Product Regulation ........................................10
Figure 2. Distribution of Years of Practice of Survey Respondents..................................24
Figure 3. Benefit and Primary Indication of PRP and BMAC Procedures..........................26
Figure 4. Primary location treated by PRP/BMAC............................................................26
Figure 5. Therapies of Interest to Respondents.................................................................28
Figure 6. Opinions on Current Regenerative Medicine Procedures.................................29
Figure 7. Opinions on Key Ingredients of BMAC and its Components..............................30
Figure 8. Ratings of Product Safety and Consistency Across Practices............................31
Figure 9. Product Dosing and Limits on Procedures..........................................................32
Figure 10. Responses on FDA regulating BMAC and PRP products.................................32
Figure 11. Instrument Manufacturer Involvement..............................................................34
Figure 12. Manufacturer Participation ..............................................................................35

Tables

Table 1. Summary of Respondent Characterization.........................................................25
Table 2. Summary of Research Related Attitudes............................................................36

Charts

Chart 1. Alternative Plan for Multi-site IND...................................................................43
Glossary

**Code of Federal Regulations.** A collection of rules and regulations set by the United States government and is published in the *Federal Registrar*. This body of laws is divided into 50 general categories or titles each subdivided further into chapters, sections, and paragraphs. These laws are enforced by the different executive branches of the government.

**Platelet Rich Plasma.** Platelet rich plasma is derived through the separation of nucleated cells from the protein and cytokine rich serum. The platelet rich plasma component is thought to have rejuvenating and healing properties. The uses are many but one of the most common is the injection into joints as a method to reduce pain.

**Bone Marrow Aspirate Concentrate.** A concentration of bone marrow cells produced as a result of removing plasma and other component from bone marrow aspirate. The resulting bone marrow concentrate pellet is comprised highly of immune cells, growth factors, as well as some stem cells. Upon concentration the bone marrow concentrate product is injected into a patient’s site of joint injury or osteoarthritis.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BMAC</td>
<td>Bone Marrow Aspirate Concentrate</td>
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<td>BMT</td>
<td>Bone Marrow Transplant</td>
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<tr>
<td>CAR-T</td>
<td>Chimeric Antigen Receptor T-cells</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
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<td>DCs</td>
<td>Dendritic Cells</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>HCTL</td>
<td>Human Cellular Therapy Laboratory</td>
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<td>HCT/P</td>
<td>Human Cellular and Tissue Products</td>
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<tr>
<td>IMPACT</td>
<td>Immune, Progenitor, and Cell Therapeutics</td>
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<tr>
<td>MSC</td>
<td>Mesenchymal Stem Cells</td>
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<td>PACE</td>
<td>Product Analysis and Component Evaluation</td>
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<td>PRP</td>
<td>Platelet Rich Plasma</td>
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<td>RMAT</td>
<td>Regenerative Medicine Advanced Therapy Designation</td>
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Chapter 1. Introduction

Regenerative medicine holds promise in the new ways to treat injuries and diseases previously deemed incurable. The Mayo Clinic has been on the forefront of moving the field of regenerative medicine forward through its development and use of biologics and cell-based therapies in both procedures and through clinical trials. As a result, new models of health care have been created transforming medicine and surgery.¹

1.1. Background

Stem cell based therapies and other biologics have gained popularity as an alternative to and as a substitute for traditional drugs. Patients with orthopedic issues, pain, sports-related injuries, and neurological and immune complications are seeking treatments such as stem cell based and regenerative medicine therapies. Procedures like bone marrow aspirate and concentrate (BMAC) as well as platelet rich plasma (PRP) are safe when appropriately utilized and have the potential to provide pain relief to those with a progressive degenerative joint disease for which alternative treatments are limited.² As part of their regenerative medicine practice Mayo Clinic physicians perform both BMAC and PRP procedures.

1.2. Statement of Problem

Regenerative medicine procedures such as BMAC and PRP are performed in multiple locations within the Mayo Clinic including Physical Medicine and Rehabilitation (PM&R), Sports Medicine, and Pain Clinic. Each practice has its own physicians and instrumentation used to perform these procedures. Physicians are given instructions regarding in how to isolate BMAC

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and PRP with regard to both instrumentation and techniques. However, there is substantial variation that can develop over time in preferences and methodologies.

Federal Drug Administration (FDA) regulations exist for biologics that fall under the category of human cellular and tissue products (HCT/Ps) (21CFR 1271). Because of recent warnings by the FDA, many practitioners in the field did not recognize that BMAC products fall under the HCT/Ps category and are regulated by the FDA. PRP products are not HCT/Ps, rather, they are a biologic agent used in regenerative medicine, thus, not regulated by 21 CFR 1271. BMAC procedures are currently not FDA approved treatments but are still under FDA jurisdiction. The FDA regulates biologics including blood and blood products, cellular and gene therapy products, and tissue and tissue products. Both BMAC and PRP fall in to these categories. These therapies have only recently become available, though there is sufficient evidence of safety and some evidence of efficacy, depending on the application. However, the evidence is insufficient to recommend widespread use of these treatments. The rapid introduction of these the processes have taken place because of regulatory interpretation of procedural use. Many of these products are generated using point of care devices. As long as the product is used in an autologous manner and in a procedural setting, there are minimal requirements associated with developing standard operating procedures, product purity and potency, supply chain control etc. These original exemptions from this regulatory framework were not intended to be applied to the in room development of biologic/cell therapies. As the

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FDA puts more effort into implementing new regulations on these developing products it is vital that those performing the procedures have an in-depth understanding of how these regulations apply to their practice and the steps that need to be taken to stay in compliance.

The regulatory confusion, the point of care use, inconsistent use by physicians, and lack of controlled trials, have resulted in a vacuum with respect to both the understanding and application of this technology. It is important to determine the knowledge base of physicians currently performing these practices and define the barriers to clinical research on patients receiving these therapies. Knowing the current behaviors of those performing these procedures assists the future development of the practice. It will provide an understanding of the current baseline of the variation among the practices and identify which areas need to be addressed if enterprise changes or harmonization efforts are made. The benefits of standardization would include ease of incorporating new technologies and educational resources, more equal comparability of patient outcomes, and ease of implementation of any new federal regulation. Therefore, it is essential to identify methods on how to move clinical research using these therapies forward. Determining the current attitudes of those performing these procedures are toward regulations, as well as their knowledge and understanding of the regulations will help identify which educational gaps need to be filled. Result of receiving FDA approval include more patients having the option of BMAC and PRP therapies as insurance companies will be more likely to cover the costs.

1.3. Project Questions

Questions used for research focused on understanding behavior through the quantity and types of regenerative medicine. In an effort to assess the attitudes towards current practices, subjects were asked to provide opinions on the current state of the market, how often procedures
could safely be performed, and what costs were appropriate for these procedures. Questions regarding regulatory oversight attempted to measure understanding of federal regulations. To determine what the main deterrents to performing research were, subjects were asked to indicate which barriers they found to be the most difficult to overcome in order to perform research. Combined, the answers to these questions characterize the practice, preferences of the practitioners, and perceptions of product efficacy, safety and regulations.

1.4. Research Objectives

In order to address the problems identified and listed in the project questions, the following objectives were determined:

1. Identify the attitudes and behaviors of physicians performing regenerative medicine procedures.
2. Determine the barriers to performing research for process improvement.
3. Analyze results and develop strategies to prepare for new FDA regulations, improve compliance, efficacy, safety, and quality of regenerative medicine products in an effort to move these procedures from research to FDA approved treatments.

1.5. Significance

This work will help identify the attitudes and behaviors of physicians currently delivering regenerative treatments and provide a baseline for developing a plan for future research and regulatory compliance. It will also provide insight into the clinicians’ decision-making processes with regard to regenerative medicine procedures. Results of the study can aid in unifying the practice, and directing appropriate education. Understanding the barriers to research will help develop a plan to address them, moving regenerative medicine research forward by gaining FDA approval for BMAC and PRP treatments, allowing for more patient to receive them.
1.6. Exclusions and Limitations

The study is limited by the small number of participants, which is a result of the number of physicians currently performing PRP and BMAC procedures at the Mayo Clinic in Rochester, Minnesota.
Chapter 2. Literature Review

2.1. Overview of Literature Review

Literature review for this work was focused on the current state of regenerative therapies as practiced in the United States. It also identified resources which would help understand how the FDA views and has been regulating regenerative medicine therapies as well as the perspectives of those practicing them. Lastly, it addressed Federal Regulations that apply to BMAC and PRP procedures.

2.2. Current Practice of Stem Cell Based and Regenerative Medicine Therapies

Regenerative medicine is a rapidly growing field based on the promise of healing to patients with difficult to treat or incurable diseases. The therapies under the regenerative medicine umbrella are vast and span from tissue engineering to stem cell and gene therapies. The effects of these treatments have been variable and currently do not have FDA approval, as there is not enough research to propel them into the category of standard of care, as proven and reliable methods for treating patients.\(^7\)

Stem cell therapies comprise a large portion of procedures in regenerative medicine practices. Stem cells have the ability to differentiate into many cell types giving them the ability to repair damaged organs and tissues.\(^8\) Other biologics such as amniotic fluid, and platelet rich plasma (PRP) have gained popularity as well.\(^9\)

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These procedures are performed by both public and private clinics and are marketed for numerous ailments. As of 2016, 351 businesses with a total of 570 clinics had been identified as performing stem cell treatments. Some of these clinics focus on cosmetic indications such as anti-aging, while others on neurological, immunological and other conditions. Sports, orthopedic, and pain clinics are the top three providers of these applications.\textsuperscript{10} Even though the science and clinical outcomes of these procedures are not well determined or understood, some clinics have been marketing “stem cell” and similar products and the like with false claims of outcomes which have yet to be proven.\textsuperscript{11} These advertisements have given vulnerable patients misleading information on the benefits and safety of these expensive treatments which can cost upwards to $12,000. \textsuperscript{12}

\section*{2.3. FDA Perspectives}

In August of 2017, the FDA brought to light the risk associated with unproven therapies as well as the adverse events that caused patients harm as a result of the “stem cell” procedures. In the released statement, FDA commissioner Scott Gottlieb promised an increase in both regulatory oversight and enforcement, providing letters of warning to clinics in Florida and California, which at a later date would be shut down by the FDA.\textsuperscript{13,14}

Regulations overseeing cell-based therapies are in existence. The Code of Federal Regulations Title 21, Part 1271: Human cells, tissues, and cellular and tissue-based products, dictates cell based therapies be treated as any other drug on the market. This includes production

\begin{itemize}
\item \textsuperscript{10} Leigh Turner and Paul Knoepfler, "Selling stem cells in the USA: assessing the direct-to-consumer industry," \textit{Cell Stem Cell} 19, no. 2 (2016): 154-157, \url{https://doi.org/10.1016/j.stem.2016.06.007}.
\item \textsuperscript{11} ibid
\item \textsuperscript{12} Piuzzi, "The stem-cell market," 551-556.
\item \textsuperscript{13} FDA, "Statement from FDA Commissioner Scott Gottlieb, MD on the FDA's New Policy Steps and Enforcement Efforts to Ensure Proper Oversight of Stem Cell Therapies and Regenerative Medicine." \textit{FDA News Release}., August 28, 2017, \url{https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm573443.htm}.
\item \textsuperscript{14} FDA, "FDA seeks permanent injunctions against two stem cell clinics." \textit{FDA News Release}, May 9, 2018, \url{https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607257.htm}.
\end{itemize}
of the cells in a GMP facility, quality control measures, and registration of the product for an IND with the FDA, and documentation of adverse events. The terms “minimally manipulated” and “more than minimally manipulated” are used to classify biological products that are human cellular and tissue products (HCT/Ps) which are subjected to the listed FDA regulations (21 CFR 1271). Complying with these regulations is time consuming and expensive, resulting in many of the clinics avoiding regulations as much as they are able. To address the issue of the definition of the terminology “minimally manipulated” in November of 2017 the FDA provided a guidance for industry that provided examples and additional information to help practitioners make informed decisions on labeling their products and understanding which regulations apply.

In February of 2019, the FDA announced the development of a new expedited program Regenerative Medicine Advanced Therapy Designation (RMAT). Unlike a full Investigational New Drug (IND) application, RMAT does not require randomized double blinded, placebo controlled clinical data, which helps expedite the approval process. (See section 2.7. RMAT Designation below for more details.)

### 2.4. Regulations Applying to BMAC Products

An exemption to 21 CFR 1271 does exist for those performing procedures in the same surgical procedure (21 CFR 1271.15(b)). An establishment that removes and implants HCT/Ps from the same patient during the same surgical procedure does not need to comply with 21 CFR

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15 21 CFR 1271
17 U.S National Archives and Records Administration, Office of the Federal Register, "Regulatory considerations for human cells, tissues, and cellular and tissue-based products: Minimal manipulation and homologous use; guidance for industry and food and drug administration staff; availability," *Federal Register* 82, no. 221 (2017): 54290-54292.
as there is no additional risk to the patient than there would be typically in surgery. The same surgical procedures as defined by the exemption are “procedures that involve an incision or instrumentation during which an HCT/P is removed from and implanted into the same individual within a single operation performed at the same establishment, are generally considered to be the same surgical procedures.” An example of this logic can be seen in Figure 1, which shows the criteria used to determine if 21 CFR 1271 applies to a specific product or does not.

This exemption provides a loophole in the system allowing invasive procedures performed in a surgical suite in one setting to be exempt. For example, a bone marrow aspirate/concentrate (BMAC) procedure during which a patient has bone marrow aspirated from the iliac crest under anesthesia, concentrated via centrifugation or separation system, followed by re-injection of the cell pellet into the joint of injury, would qualify for this exemption. Using the guidance provided, the FDA states that PRP is not considered HCT/P and thus is not covered under 21 CFR1271.

As noted in the Background section of this document, this guidance only applies to products and establishments that are subject to FDA’s regulations in 21 CFR Part 1271. Establishments that meet the same surgical procedure exception in 21 CFR 1271.15(b) are not subject to FDA’s regulations in 21 CFR Part 1271. This guidance also does not apply to products that fall outside the definition of HCT/P in 21 CFR 1271.3(d). For example, platelet rich plasma (PRP, blood taken from an individual and given back to the same individual as platelet rich plasma) is not an HCT/P under Part 1271 because it is a blood product. Accordingly, FDA does not apply the criteria in 21 CFR 1271.10(a) to PRP, and PRP is outside the scope of this guidance.

As for BMAC procedures, regulations are not as clear. Same day surgical procedure would appear to apply to BMAC procedures, but the Same Surgical Procedure Exception does respond to the following question “Can an establishment that processes an autologous HCT/P after

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20 ibid
21 Federal Register 82, no. 221 (2017): 54289-54290
removal and prior to implantation still qualify for the exception in 21 CFR 1271.15(b)?” with this answer:

In general, limited handling such as rinsing and cleansing, by centrifugation or filtration solely to remove debris (e.g., lipids, blood, bone particles) would allow the HCT/P to remain “such HCT/P.” Other processing steps, including by centrifugation or filtration, for cell isolation, cell expansion, cell activation, or enzymatic digestion generally would not allow the HCT/P to remain “such HCT/P” and the establishment would not qualify for the exception.22

Given bone marrow once aspirated is centrifuged for plasma removal and in some cases other cell types, may not qualify for this exemption depending on the purpose and specifics of the procedure.


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22 ibid
2.5. Regulations Applying to PRP Products

Title 21 also regulates PRP but rather part 640 Additional Standards for Human Blood and Blood Products, Subpart D – Plasma. Section 640.34 describes the appropriate processing procedures for plasma including the appropriate process of collection and preservation. Platelet Rich Plasma is specifically discussed:

(d) Platelet Rich Plasma. Platelet rich plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within 4 hours after completion of the phlebotomy or within the timeframe specified in the directions for use for the blood collecting, processing, and storage system. The time and speed of the centrifugation shall have been shown to produce a product with at least 250,000 platelets per microliter. The plasma shall be stored at a temperature between 20 and 24 deg. C immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20 to 24 deg. C.

2.6. Disagreements in Interpretation of FDA Regulations

Due to the lack of clarity provided by the FDA, opinions have been split if BMAC procedures fall under “Same Day Surgical Procedure Exemption” or if they do not. The regulatory loophole leaves three areas or problems that should be addressed as described by Paul Knoepfler in 2017.

The organization of the SSPE decision-making flow chart is not clear on what should happen if a procedure qualified for SSPE but also does not meet criteria for HCT/P. With regard to this question, Knoepfler inquired of the FDA if “non-homologous uses nullify a potential same-day surgical exception?” In response, the FDA stated that yes, homologous use is independent of the SSPE determination, and is not considered when determining if the product applies for the exemption. This would indicated that an HCT/P as long as it falls under SSPE

24 21 CFR 640
could be used in a non-homologous manner, which could potentially have a harmful outcome to patients if the product was injected into any given site.\textsuperscript{25}

Terms “minimally manipulated” though provided with a definition by the FDA, still lack clarity. To qualify as “minimally manipulated” the product must not “alter the relevant biological characteristics of cells or tissue”.\textsuperscript{26} The centrifugation and separation processes typically used for BMAC procedures are capable of removing red blood cells, granulocytes, platelets, plasma, and other unknowns during the process. Additionally, adding anticoagulant and centrifuging cells at high speeds could also possibly have an effect on them. It can be argued that procedures such as BMAC that involve an intense separation processes are more than minimally manipulated.\textsuperscript{27}

What qualifies a procedure to be a “surgical procedure” could also be debated. As previously stated, “procedures that involve an incision or instrumentation during which an HCT/P is removed from and implanted into the same individual within a single operation” are typically considered a surgical procedure. Some may have differences in their interpretation of this definition.

2.7. National and International Society Perspectives on Regenerative Stem Cell Therapies

Multiple international societies have stated their expectations for how regenerative stem cell therapies should be monitored. Following are discussions of the perspectives of three societies involved in cell therapies.


\textsuperscript{26} Human Cells, Tissue, and Cellular and Tissue based Products; Establishment Registration and Listing” 66FR 5447 and 5457 (January 19, 2001.).Tissue Registration and Listing; Final Rule.)

2.6.1. International Society for Cell and Gene Therapy Perspective

The International Society for Cell and Gene Therapy (ISCT) focuses on the collaboration between academic, regulatory, and commercial entities in an effort to translate cell and gene based therapeutics into medical treatments for patients by leading research into standard of care. ISCT has designated a Presidential Task Force (PTF) on “The Use of Unproven and/or Unethical Cell and Gene Therapy” to identify unproven cell therapies and help investigators appropriately move therapies forward. In an effort to educate about the current events regarding cell and gene therapy documents and news announcements regarding these topics are posted on the society webpage.28

2.6.2. International Society for Stem Cell Research Perspective

The International Society for Stem Cell Research (ISSCR) provides guidelines for stem cell research and clinical translation. With regard to review and oversight of cell based products, the society states that oversight should be proportionate to the risk induced from the manipulation of the cells. For products that fall under the minimally manipulated category, ISSCR notes that the practitioner is responsible for scrutinizing the product and work performed but no definite standards are provided for procedures or quality control.29

2.6.3. AABB Perspective

AABB seeks to make safe transfusion medicine and cellular therapies to donors and patients by working closely with the FDA through input regarding the technical and developmental aspects of the therapies. For example the AABB provided comments to the on

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“Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products; Draft Guidance for Industry and Food and Drug Administration Staff” in 2015.\textsuperscript{30} \textsuperscript{31} Although the organization’s initial focus was on blood banks it now includes transfusion medicine and cell therapies.\textsuperscript{32} No specific guidelines are provided for BMAC products.

\textbf{2.8. RMAT Designation}

The RMAT designation is developed to aid those treating serious or life-threatening disease or conditions by expediting the approval process for their regenerative medicine treatment. This designation falls into the same category as FDA’s other expedited programs such as “fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation”. Products can have approval requested for multiple designations but each must be submitted independently and follow the appropriate standards for approval (See FDA Chart). An IND must still be submitted to receive the RMAT designation but additionally the proponents must also submit a request to the Center for Biologics Evaluation and Research (CBER). Eligibility criteria for RMAT include:

1. It meets the definition of regenerative medicine therapy

2. It is intended to treat, modify, reverse, or cure a serious condition; and

3. Preliminary clinical evidence indicates that the regenerative medicine therapy has the potential to address unmet medical needs for such condition.\textsuperscript{33}


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As of 2018, 43 RMAT requests were submitted to the FDA. Of these 22 were denied, 15 were granted and the rest still pending. Denied requests were due to “inactive IND, lack of preliminary clinical evidence, study design issues, and inconsistent results with regard to product activity.”

Of the 43 requests 8 were from academic and non-profit settings while the rest were from commercial entities. Further, over 50% of the products were autologous cell therapy products while 30% were allogeneic cell therapy products.  

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Chapter 3. Project Description

The market for “stem cell” therapies and other regenerative medicine treatments has grown substantially, but with this growth several challenges have emerged. Although FDA regulations for cells that have been more than minimally manipulated are clearly defined, but, it is not well understood as to which products are covered under the terms “minimally manipulated”. Additionally, even though these types of therapies appear to be promising, data is still lacking on the effectiveness of these treatments.

This project focuses on the regenerative medicine procedures of PRP and BMAC at the Mayo Clinic and how FDA regulations apply to these procedures. As both PRP and BMAC are not yet approved by the FDA, this project also seeks to identify the steps necessary to move them towards approval.

A survey questionnaire was created to help address these issues. The data collected was used to understand the baseline behaviors and attitudes. By doing so, gaps in understanding regulations could be identified and a plan could be developed to address them.
Chapter 4. Need(s) Assessment

4.1. Establishment of the Need

In 2017 the FDA issued a statement calling out “bad actors” who had capitalized on the potential of regenerative medicine and “stem cell” therapies by making false claims to vulnerable patients by over-promising what the products can deliver as well as their safety. Descriptions of steps taken, such as warning letters sent to clinics marketing particularly troubling products, were described in the statement with guarantee of more enforcement action to follow. In the same statement, the FDA ensured that new regulatory frameworks would be established, providing clarity on how regenerative medicine products are regulated. This statement was a wake-up call for many practicing regenerative medicine. Even for institutions such as Mayo Clinic the FDA’s statement, brought extra attention on validating that the procedures performed met regulations and also served as a reminder that these therapies were still not FDA approved.35

The Human Cellular Therapy Laboratory (HCTL) at the Mayo Clinic in Rochester, Minnesota, develops, manufactures, and distributes cell-based products at the institution. HCTL has two programs, the Bone Marrow Transplant (BMT) as well as the Immune, Progenitor, and Cell Therapeutics (IMPACT) program. Both have been developed in compliance with all federal regulations. Cell products developed in IMPACT include dendritic cell vaccines (DCs), mesenchymal stem cells (MSCs), and chimeric antigen receptor T cells (CAR-Ts).36 In order to comply with 21 CFR 1271, all cell products go through the process of acquiring INDs, are produced in GMP facilities, and must pass extensive quality control criteria prior to being

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35 FDA, "Statement from FDA Commissioner Scott Gottlieb, MD on the FDA's New Policy Steps and Enforcement Efforts to Ensure Proper Oversight of Stem Cell Therapies and Regenerative Medicine."
released to the patient. IMPACT lab’s experience with testing and characterizing cell-based products ignited collaboration with those performing PRP and BMAC procedure. As a result of this partnership a new program developed, Product Analysis and Component Evaluation (PACE). At this time, samples from clinical BMAC procedures performed in the PM&R and sports medicine practices are sent to PACE to identify the product’s cell populations determine the calculated cell dose given to the patient. During the initiation and the course of the collaboration it was recognized that instrumentation as well as techniques used to perform the procedures varied between providers. It was observed that the departments providing PRP and BMAC used different types of instrument for manufacturing. For example, Sports Medicine used the Biomet systems, the pain practice used the EmCyte system, and PM&R used the Arthrex Angel system. Further complicating the situation, some patients had bilateral procedures performed during which two sites were injected as opposed to the typical single injection. The methods for aspirating the bone marrow varied between the providers, some using drills while others used manual trocar needle and cannula. For those using the Arthrex Angel system when performing bilateral large joint procedures (e.g. bilateral knee injections) some providers used one kit while others chose to split their products into two.

4.2. Metrics Used to Establish the Need

The need for this work was recognized by the author through observations during the development process of the PACE program as well as its current continuing partnership. During development, the BMAC process was compared to the current FDA regulated MSC process with regard to quality control and release criteria. From this, questions of how the BMAC products were dosed, and how their components were evaluated arose. Additionally, as more locations were added to the PACE program differences in methodology became more apparent. When
considering options for research, these variations in practice limited the extent of the research. In an active manuscript preparation, the author and PACE collaborators noticed that when compiling data for research the groups used for comparison were not as robust as they could have been if there were fewer differences among the procedures.

4.3. Sources Consulted at Institution to Establish the Need

The scientific director of the IMPACT lab as well as the Vice Chair of Physical Medicine and Rehabilitation who both spearheaded the development of the PACE program were consulted. The scientific director of IMPACT has had significant experience in the development of cell therapies as well as their implementation into the clinic under FDA regulations. The Vice Chair of Physical Medicine and Rehabilitation practices PRP and BMAC procedures in both departments of PM&R and Sports Medicine and has been overseeing development of manufacturing procedures and clinical research in these areas.
Chapter 5. Methodology

5.1. Methodology Overview

The objectives of the work were three-fold. First it was important to establish where the practice at Mayo currently stands with both regards to the methodologies used by those performing PRP and BMAC procedures and understanding of Federal Regulations that apply to their work. Secondly, it was necessary to establish the reasons for why physicians are not performing more research that is necessary to move these products into a standard of care. Lastly, an analysis of the answers for the previously mentioned goals was performed in order to create a plan on how to move the field forward in both research and regulatory application.

Data collection for this project was primarily acquired through a questionnaire survey. Information needed to design the survey was obtained through literature search and through observations during the development of the PACE program. The interactions during this development process allowed for insight into the current operations of the institution with regard to PMR and BMAC procedures, as well state of the practice at a local level. The questionnaire was given to those practicing PMR and BMAC procedures. The results were compiled and major behaviors and attitudes were established from this data. Reports for moving forward in compliance with new FDA regulations were designed by analyzing the current practice behaviors, trends and other information found in the literature search, and through the application of Federal Regulations.

5.1. Project Design

The design of the project methods could be separated into very clear, logical steps. First the focuses of the project were identified based on observations from the practice and FDA announcements regarding the work. Next, background information was collected through an in-
depth literature search. A questionnaire was developed based on both the literature search and the observations. The questionnaire was reviewed by two individuals at the Mayo Clinic and one at Johns Hopkins University to verify the appropriateness and clarity of the questions. The survey was sent out to 10 physicians with hopes of receiving a 70% response. Lastly, the results were compiled and conclusions determined based on the answers provided.

5.3. Project Discussion

The layout of the project was such that both background information through the literature search and the questionnaire were of equal importance. The literature search had three main components; current practices, issues in the field, and Federal Regulations. The problem of mis-marketing of stem cells in the field as well as common misunderstandings of how and which FDA regulations apply to these practices are well discussed in Chapter 2. Literature Review in this paper. This included an in-depth analysis of the regulations with a focus on 21CFR 1271, exemptions, FDA warning letters, additional explanations, and any new applicable regulations was performed to verify what was applicable to the practice. Discussion of suggestions for how to best implement these regulations were examined to see if any would be logical to implement.

Aside from the literature search, for this project it was important to understand how the practice at Mayo was structured, its function, and what the variables were among those performing PRP and BMAC procedures. This information was collected through the observations from the development and the execution of the PACE program which allowed for collaboration with the necessary individuals and an in-depth understanding of how the procedures were performed.

The questionnaire was sent to a total of 10 participants with the response rate of 80%. Survey Monkey was used as the instrument for collecting the participant answers. Survey
Monkey allowed for the results to be collected in an anonymous manner with the IP address and email address not being able to be traced back to the used. The study was reviewed by both Mayo Clinic and Johns Hopkins University Institutional Review Boards both classifying it as exempt. Due to the small group of participants who were employed by the same institution, it was necessary to take extra measures to maintain confidentiality, including exporting results in batch, and excluding any questionnaire results that could unmask identities being deduced due to small cohort size.

5.4. Discussion of Questionnaire

The purpose of the questionnaire was to address the topics of behaviors, and attitudes, and challenges to performing research. The Questionnaire may be found in Appendix 1. Questions asked were separated into 6 specific subsets. The first questions of the survey were used to verify that the participant met the criteria of the study and to determine their level of experience. The second portion of the questionnaire (questions 4-9) was developed to gain a better understanding of what methods were used to perform the procedures of interest and the purpose for which they were used. The following questions (10-20) were meant to ascertain opinions and attitudes towards the therapies broadly as well as impressions regarding their safety, functionality, and benefit. Additional questions obtained information regarding how the therapies work, as well as involvement of the FDA and companies developing the equipment were meant to measure the understanding of current regulations (questions 21-30). The last set of questions sought to determine the barriers for performing research (questions 31-36). The questions were purposefully written in a fashion that would allow for the survey to be able to collect data outside of the institution in future studies.
Measurements used to assess the questions varied on the type of question being asked and the options provided. Most questions asked provided a multiple choice answer to reduce the types of responses for answers and decrease the amount of time it would take for the subjects to complete the survey.
Chapter 6. Project Results

6.1. Survey Questionnaire Results: Participant and General Practice Information

Survey results were obtained via Survey Monkey using an anonymous collection method. The survey invitation was sent to the original 10 subjects on day one and a reminder email sent four days after the initial invite. Final response rate to the survey was 80%. All respondents were physicians who had been practicing 6 to 20+ years (Figure 2 and Table 1). Of the respondents, 25% performed PRP procedures while 75% performed both BMAC and PRP. No respondents performed BMAC procedures alone. Those performing BMAC did so 1-5 times per month with all preferring to use the Emcyte (16.67%) or Arthrex Angel (83.33%) concentrating systems. PRP procedures were performed 1-5 times per month by 37.5% of participants, 6-10 by 25%, 11-15 by 25%, and 15-20 by 12.5% (Table 1).

Figure 2. Distribution of Years of Practice of Survey Respondents
Establishing baseline data regarding who performs PRP and BMAC procedures and how they perform them is essential to understanding the current practice at Mayo Clinic. The data collected were reflective of multiple locations as the participants practiced across the institution in different areas. Of those that responded to the survey invite and provided feedback, all were physicians who had been practicing for 6 or more years and performed PRP procedures, a majority 1-10 times per month (62.5%) or 11-20 (37.5%) times per month. BMAC procedures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Respondents</td>
<td>n=8</td>
</tr>
<tr>
<td>Current Position at Practice</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>100%</td>
</tr>
<tr>
<td>Fellow</td>
<td>0%</td>
</tr>
<tr>
<td>Resident</td>
<td>0%</td>
</tr>
<tr>
<td>Years of Practice (Physician Specific)</td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>0%</td>
</tr>
<tr>
<td>6-10</td>
<td>50%</td>
</tr>
<tr>
<td>10-15</td>
<td>25%</td>
</tr>
<tr>
<td>15-20</td>
<td>12.50%</td>
</tr>
<tr>
<td>20+</td>
<td>12.50%</td>
</tr>
<tr>
<td>Distribution of Procedures Performed</td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td>25%</td>
</tr>
<tr>
<td>BMAC</td>
<td>0%</td>
</tr>
<tr>
<td>Both PRP and BMAC</td>
<td>75%</td>
</tr>
<tr>
<td>Times per Month Procedure is Performed</td>
<td></td>
</tr>
<tr>
<td>Procedures/month</td>
<td>PRP</td>
</tr>
<tr>
<td>1-5</td>
<td>37.5%</td>
</tr>
<tr>
<td>6-10</td>
<td>25.0%</td>
</tr>
<tr>
<td>11-15</td>
<td>25.0%</td>
</tr>
<tr>
<td>15-20</td>
<td>12.5%</td>
</tr>
<tr>
<td>20+</td>
<td>0.0%</td>
</tr>
<tr>
<td>Instrument of Preference (BMAC Procedures)</td>
<td></td>
</tr>
<tr>
<td>Biomet</td>
<td>0%</td>
</tr>
<tr>
<td>Angel Arthrex</td>
<td>83.33%</td>
</tr>
<tr>
<td>Emcyte</td>
<td>16.67%</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 1. Summary of Respondent Characterization
were performed by 75% of the respondents, all stating an average of 1-5 procedures per month. From this, it can be concluded that the total number of PRP procedures being performed at the institution per month is between 57 to 85+, and number of BMAC procedures between 6 and 30. There were many similarities among the respondents, such as instrument of preference (Arthrex Angel), times per month PRP and BMAC are performed, and years of practice (75% stated 6-15 years). This information indicates that even though these procedures are being performed in different locations, the practices have very similar characteristics.

6.2. Survey Questionnaire Results: Procedures and Patient Benefit

Questions regarding the specifics of the procedures and observations of patient benefit were asked in order to better understand the practice and procedure outcomes. Twenty percent of those surveyed believed that 25-50% of patients receiving BMAC benefited from the procedure, 60% believed 50-75% of patients benefitted, and 20% believed 75-100% benefitted. Alternatively, 28.57% believed PRP benefitted 25-50% of the patients, 42.86% believed 50-75% benefitted, and 28.57% believed 75-100% benefitted (Figure 3). The primary indication for which the respondents used BMAC was orthopedic or musculoskeletal issues (non sports related).

Figure 3. Benefit and Primary Indication of PRP and BMAC Procedures (A. Response distribution of percent of patients benefitting from PRP/BMAC as observed by respondents B. Most common injuries treated by PRP/BMAC)
(66.67%) and pain (33.33%). Similarly, PRP was used for orthopedic or musculoskeletal issues (non sports related) (62.5%), pain (25%), but also sports injuries (12.5%) (Figure 3). BMAC procedures performed were either to the knee (75%) or back (25%), while PRP procedures to the knee (75%), back (12.5%) or “other” (12.5%), which respondents expanded upon and specified as tendons and ligaments (Figure 4).

![Figure 4. Primary Location Treated by PRP/BMAC](image)

PRP procedures were primarily used to treat orthopedic/ musculoskeletal injuries (62.5%) or pain (25%) and predominately performed on the knee (75%). It can be concluded that PRP and BMAC procedures across the institution are predominately used to treat articular knee disorder such as arthritis and meniscal tears.

Opinions pertaining to the potential benefits of PRP to the patient were variable but most respondents (71%) indicated that over 50% of patients benefitted from the procedure. In comparison, BMAC procedures were also primarily used for orthopedic/ musculoskeletal injuries (66%) or pain (33%) and once again primarily on the knee (75%). Of the physicians, 80% believed that BMAC benefitted over 50% of the patients. The high rates of observed benefit to patients from these procedures is a valuable finding. Since respondents believe that these therapies work, it is more likely that they will be willing to enroll patients into clinical trials.
using PRP and BMAC and participate in other efforts needed to continue being able to perform them.

6.3. Attitudes: Product and Procedures Safety, and Current Market

In order to assess the safety of the products currently on the market compared the standard treatment and other treatment options, the respondents were asked to rate the following in order of safety (1 lowest safety- 10 highest safety): BMAC, PRP, cord blood, amniotic fluid, placental products, steroids, approved biologics (ie Enbrel), surgery, and joint replacement. Based on the average rating given, the products/procedures were rated as follows from lowest to highest in safety: cord blood (3.625), amniotic fluid (3.625), joint replacement (3.875), surgery (4.375), placental products (5.125), approved biologics (5.25), BMAC (5.75), steroids (6.5), and PRP (6.875).

Respondents were asked to indicate if they had the freedom to do so what other therapies they would try. The responses reflected an interest in cord blood (25%), amniotic fluid (25%), placental products (12.5%) and “other” (37.5%) which included lipoaspirate/ micro-fragmented fat, A2M (alpha-2-Macroglobulin), and ACS (autologous conditioned serum) a form of PRP (Figure 5).

Figure 5. Therapies of Interest to Respondents
Even though participants expressed an interest in trying other biologics on the market such as cord blood and amniotic fluid they scored both products nearly equal to joint replacement in terms of safety, but less safe than surgery, placental products, approved biologics, BMAC, steroids, and PRP. Over all perceptions indicate that providers associate risk to the patient with both cord blood and amniotic fluid products. Both products, unlike PRP and BMAC, are not autologous, and would need to be used with greater caution and have added testing to verify safety.

When asked if new FDA regulations regarding regenerative treatments will be beneficial to the respondent’s practice or if they will not, 100% of respondents stated that regulations would benefit their practice. These results could reflect the effects of tighter regulations such as a likely decrease the number of regenerative medicine providers in the United States, as not all would be able to meet the criteria, thus funneling patients to clinics that can. Another effect would be the increase in safety standards, which would benefit the patients by reducing risk.

In total 37.5% feared that not performing BMAC and PRP procedures would jeopardize their practice, while 75% stated they believed patients would go elsewhere if BMAC procedures were referred to without using the terms “stem cells”. All participants responded that they would suggest BMAC and PRP procedures to a family member or have one performed on them indicating their belief in the safety of the products (Figure 6).
To determine which component of bone marrow respondents considered to be responsible for the product’s healing capacity, the questionnaire asked which of the following respondents believed was the key ingredient: cytokines, platelets, WBCs, RBCs, or stem cells. The responses showed 71% believed cytokines were the key ingredient, while 14% indicated platelets, and 14% indicated stem cells. When asked which values most appropriately reflected the contents of bone marrow 85.7% responded 1% stem cells with 99% WBC/RBC, and 14.3% stated 5% stem cells with 95% WBC/RBCs (Figure 7).
Respondents generally believed that the current mis-marketing for regenerative therapies is fully driven by profit and that the term “stem cells” is which is the key in advertisement and is used as a mechanism of attracting patients. Even though when asked what the key ingredient is in BMAC is, most believed it was cytokines (71%) rather than stem cells (14%) (which all understood to be a small portion of bone marrow). However, 75% acknowledged that if the term “stem cells” was not used patients would go elsewhere for treatment. This information shows the need to perform research in order to determine what the true key ingredients are in these regenerative medicine therapies and educate patients appropriately.

6.4. Assessment of Safety and Current Regulations

Responses showed that the consistency and safety of the products across practices were rated highly with average scores of 8 for BMAC and 9.25 for PRP. Consistency ratings were more variable with BMAC an average of 4.33 and PRP with an average of 4.875 (Figure 8).

![Figure 8. Ratings of Product Consistency and Safety Across Practices](image)
A fundamental aspect of drug production is dosing, which in the case of BMAC procedures is a difficult to do. All respondents indicated that “whatever is produced” in the dose for BMAC procedures (Figure 9). This is likely due to the technical difficulty of obtaining bone marrow, and value of the product (which is unknown and not a topic of the current study). Thus dosing does not appear to be a factor in the current application of BMAC.

All participants stated that they inject all the concentrate produced by the kit but noted that across practices the product consistency varies (4.33/10). With regard to how often a BMAC procedure can safely be performed 50% responded with no limit and 50% with once every 6 months. On the other hand, 62% stated that PRP procedures were safe to perform without limit, while 25% said once a month, and 12.5% once every 6 months (Figure 9). Even though responses were fairly similar on how many times a patient can have the procedure, there appears to be no consensus across the practices.

<table>
<thead>
<tr>
<th>How do you dose your products?</th>
<th>BMAC</th>
<th>PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Don't dose</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Use whatever is produced by the kit</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Nucleated cell count</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Other</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>How often can a patient safely have BMAC/PRP procedure performed?</th>
<th>BMAC</th>
<th>PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No limit</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>Once per month</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>Once every 6 months</td>
<td>50%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Once per year</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Once every 2 years</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Once every 5 years</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Figure 9. Product Dosing and Limits on Procedures
Respondent opinion was gathered on FDA regulating BMAC and PRP products. Results were equal with respect to whether the FDA should regulate PRP (50% yes, 50% no) on PRP while 75% believed that BMAC products should be regulated while 25% did not (Figure 10).

Most respondents (75%) stated that BMAC procedures should be regulated, which is perhaps a reflection of the complexity of the procedure and increased risk to patient in comparison to that of PRP. Nonetheless, all respondents agreed that new FDA regulations would be beneficial to the practice, indicating openness to change.

6.5. Attitudes: Instrument Manufacturers

Respondents were asked to rate their understanding of how their instruments work to concentrate BMAC/PRP products, 37.5% responded they were extremely familiar, 37.5% very familiar, and 25% somewhat familiar (Figure 11). When asked if the companies that distribute these instruments make them aware of improvements made to the machines 62.5% said yes and 37.5% said no (Figure 11).
Those that responded yes were asked how well they understood how these improvements translate into better use of BMAC/PRP (Figure 12).

Figure 11. Instrument Manufacturer Involvement (A. Level of familiarity with instrument B. Company communication of instrument improvements to provider)

Figure 12. Manufacturer Participation (A. Respondent understanding instrument improvement translation into better use B. Attitude towards manufacturers needing to demonstrate product safety and efficacy)
Results varied from not at all (20%), a little (20%), a moderate amount (40%) to a lot (20%). Most (87.5%) believed that the manufacturers of the devices are responsible for demonstrating product efficacy and safety (Figure 12). Results of instrument manufactures’ presence with regard to performance of procedures and education on instrumentation were difficult to assess given the variability in answers provided to questions addressing this area. It appears that most providers understand how their instrument functions but interactions with manufacturer are not significant. However, most providers feel that demonstrating product efficacy and safety is a responsibility of the manufacturer.

6.6. Attitudes: Research

Participants were asked if they thought BMAC/PRP procedures would become a standard of care. Most answered that yes, within the next 10 years they will (75%). The remainder responded that they will become a standard of care sometime many years in the future (25%), and none responded with “never”. However, in order for this to happen, research on BMAC and PRP must be performed. Thus it can be concluded that the respondents are aware of the need for research and expect research to be performed in the next few years. In an effort to understand the current barriers for performing research, respondents were asked to identify them. The most commonly identified barriers to performing research in the area of regenerative medicine were time (37%), financial support (37%), and difficulty in tracking patients over time (25%) (Table 2).

A main component of research is standardizing patient outcomes. The most reliable method for measuring patient outcomes was believed to be patient survey/patient reported outcomes (75%) and clinical evaluation of the patient (25%). The agreement across practitioners
for outcome measurements would simplify an institution-wide study, which results indicate is mostly the case.

Most respondents (87.5%) indicated that they were aware of randomized controlled double blind studies showing efficacy of BMAC or PRP, whereas the remainder (12.5%) did not (Table 2). Respondents were asked what would they do if a double blind study showed no efficacy for BMAC/PRP but also no adverse events. Most responded that they would keep using BMAC/PRP but wait for more studies to clarify the subgroup in which the products it would work (75%) whereas the minority of respondents would discontinue offering the product based on the results (25%). If the outcomes of the research performed on the products did not support efficacy or were negative 37% of respondents believed that this would be a detriment to their practice, and 63% did not. Lastly, the respondents were split on who should support the ongoing improvement of these technologies, 37.5% identified the companies developing the technologies, 37.5% the government/federal agencies, and the remaining 25% medical institutions (Table 2).

In an effort to understand how the results of randomized controlled double blind studies would influence the practice, feedback was collected on possible outcome scenarios. In a situation where the study showed no efficacy for BMAC/PRP products but also no adverse events, most (75%) said they would continue using the products until stronger results were collected. This is most likely a reflection of the respondents’ observations of positive procedure outcomes. In another case, where research either did not support efficacy or had negative results, 63% believed this would have no detrimental impact on their practice. The result of this scenario would indicate that the therapy functions as a placebo thus the reason for outcome is unclear and would need further investigation to clarify.
Table 2. Summary of Research Related Attitudes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opinion on BMAC/PRP becoming a standard of care?</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0.0%</td>
</tr>
<tr>
<td>In the next 10 years</td>
<td>75.0%</td>
</tr>
<tr>
<td>Sometime many years in the future</td>
<td>25.0%</td>
</tr>
<tr>
<td>What is the most reliable method for measuring patient outcomes?</td>
<td></td>
</tr>
<tr>
<td>X-ray</td>
<td>0.0%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>0.0%</td>
</tr>
<tr>
<td>Clinician evaluation of patient</td>
<td>25.0%</td>
</tr>
<tr>
<td>Patient survey/patient reported outcomes</td>
<td>75.0%</td>
</tr>
<tr>
<td>What do you find to be the biggest detriment to performing research in this area?</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>37.5%</td>
</tr>
<tr>
<td>Financial Support</td>
<td>37.5%</td>
</tr>
<tr>
<td>Lack of appropriate participants</td>
<td>0.0%</td>
</tr>
<tr>
<td>Tracking patients over time</td>
<td>25.0%</td>
</tr>
<tr>
<td>Other</td>
<td>0.0%</td>
</tr>
<tr>
<td>If the outcomes of research performed on the products do not correlate with patient outcomes or are negative, do you believe this will be detrimental to the practice?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37.5%</td>
</tr>
<tr>
<td>No</td>
<td>62.5%</td>
</tr>
<tr>
<td>Are you aware of prospective, randomized controlled double blind studies showing efficacy of BMAC or PRP?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>87.5%</td>
</tr>
<tr>
<td>No</td>
<td>12.5%</td>
</tr>
<tr>
<td>If a double blind study showed no efficacy but also no adverse events, what would you do?</td>
<td></td>
</tr>
<tr>
<td>Keep using but wait for more studies to clarify the subgroups it would work</td>
<td>75.0%</td>
</tr>
<tr>
<td>Stop using it</td>
<td>25.0%</td>
</tr>
<tr>
<td>Use it only if the patient demands it</td>
<td>0.0%</td>
</tr>
<tr>
<td>Who should support the ongoing improvement of these technologies?</td>
<td></td>
</tr>
<tr>
<td>Medical Institutions</td>
<td>25.0%</td>
</tr>
<tr>
<td>Companies developing these technologies</td>
<td>37.5%</td>
</tr>
<tr>
<td>Government/ Federal Agencies (e.g. NIH, DOD)</td>
<td>37.5%</td>
</tr>
<tr>
<td>Private donors</td>
<td>0.0%</td>
</tr>
<tr>
<td>Other</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Chapter 7. Recommendations and Conclusions

7.1. Introduction

The purpose of this study was to develop an understanding of the attitudes and behaviors of those performing regenerative medicine point of care PRP and BMAC procedures at the Mayo Clinic. By collecting information on procedure specifics and clinicians’ preferences, baseline attitudes could be determined, preferences and knowledge base of those performing these point of care procedures. Due to the possible increased oversight of BMAC procedures by the FDA, it was valuable to understand where the participating providers stood on the matter and how they perceived the performance of regenerative medicine across practices. Obtaining this information was helpful in developing a plan for possible necessary compliance with Federal regulations. Lastly, to understand what hindered the participants from performing research, information was gathered on the main barriers of doing so, current knowledge of studies being performed, and possible responses to certain outcomes. Together, the data collected with its interpretation provided a comprehensive understanding of the current state of the practice with regard to these specific point of care procedures at the Mayo Clinic and insight on thoughts and opinions on moving the procedures forward to regulatory compliance and standard of care.

Recommendation 1: Addressing Barriers to Research

The main barriers to performing research were identified as time needed to perform the research (37%), financial support necessary (37%), and the difficulty in tracking patients over time for outcome measurements (25%). The amount of time necessary to perform research is substantial and can be extremely challenging given physicians’ schedules and responsibilities. For this reason research support staff are necessary to identify subjects, enroll, and consent
appropriate patients as well as follow up and oversee necessary documentation. Currently many departments at Mayo Clinic have their own study support staff including coordinators, research technologist, research scientists, and registered nurses. Utilizing these resources could be one method to reducing the amount of time necessary to perform research. Financial support can be acquired through a variety of methods. The most likely to be funded are request for internal funding from the institution and funding from the NIH.

**Recommendation 2: Strategies for Implementation of New FDA Regulations**

The FDA has stated that it will allow those developing and using regenerative medicine 36 months from November 16, 2017 to determine if they need to apply for an IND. If yes, then they must do so within the given timeframe.\(^{37}\) After assessing the current guidance documents and regulations that pertain to BMAC and PRP products two conclusions could be made. First, PRP does not fall under 21 CFR 1271, meaning new FDA regenerative medicine regulations will not apply. Secondly, it is not entirely clear how the FDA views BMAC products given that it could be argued both ways in terms of minimally manipulated or not minimally manipulated. Assuming that BMAC products will continue to be deemed minimally manipulated or be shielded by the same surgical procedure exemption is a risky assumption. If the outcomes of such an assumption prove to be incorrect, the repercussions would be damaging to the practices and institution with respect to time, money, and credibility, potentially jeopardizing the practice.

In an effort to avoid possible regulatory conflicts, it is recommended that the practice apply for an IND for BMAC procedures before the time expires. The FDA has provided a comprehensive framework for regenerative medicine that includes expedited and efficient new ways to request IND approval. The traditional and alternative plans for receiving a biologics

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license are described by Peter Marks and the director of the FDA Scott Gottlieb in a special report in the *New England Journal of Medicine*.\(^{38}\) The traditional development of biologic drugs involves a single manufacturer of a product, tested at multiple trial sites, resulting in a single biologics license issued, the alternative plan allows for multiple manufacturing sites producing drugs using the same protocol, each site enrolls their own patients, results are collected and each site receives their own IND. When comparing the two plans in the context of BMAC procedures, the latter would appear to be the more appropriate choice. Where typically a drug would need to be manufactured, a BMAC product would not, thus having a single manufacturing site would not be feasible.

Based on the protocol described by Marks and Gottlieb, the first step in the process is to develop a cooperative agreement among the sites (Chart1). It is suggested that Mayo Rochester oversees this aspect of the plan as most of the procedures and administrative resources are located on the Rochester campus. One single protocol must be written and used by all of the sites. As observed from the behavioral survey, a majority of BMAC procedures are performed on the knee for orthopedic or musculoskeletal indications using the Arthrex Angel separation systems, which may be an ideal starting point for developing the protocol. Creating a protocol that would encompass most of the procedures currently being performed in the manner they are performed would provide for easier implantation. Standards set by the FDA require GMP, GTP, and GCP to be followed during the drug manufacturing process. All three must be reviewed and implemented over the multiple sites. An IRB specific to the study but including all participating sites must be in place prior to patient enrollment. Patient enrollment would be site-specific but data used to evaluate safety and product efficacy must remain uniform for proper analysis. Once the manufacturing protocol has been developed, clinical data obtained for each site, and results

\(^{38}\) ibid
collected showing safety and efficacy, a site-specific biologic license for the group can be submitted. In an effort to expedite the process, it is suggested that an application for an RMAT designation is submitted as well.

Chart 1. Alternative Plan for Multi-site IND (as described by Marks and Gottlieb in "Balancing Safety and Innovation for Cell-Based Regenerative Medicine" New England Journal of Medicine with suggestions of actionable steps throughout the process)
Conclusion

The popularity of point of care regenerative medicine procedures has grown substantially with procedures being available at large institutions such as Mayo Clinic and also small private clinics around the United States. The quality and safety of the products being offered varies greatly and regulatory oversight is actively pushing those providing services to comply with appropriate FDA policies. Mayo Clinic currently provides both PRP and BMAC procedures for their patients at different departments throughout the institution. Even though deemed safe by those performing them in the absence of a controlled clinical trial, BMAC procedures could still be required to be regulated by the FDA and would need an IND in order to continue to provide them.

As it stands, both PRP and BMAC are still considered experimental therapies and not yet approved by the FDA due to lack of evidence of their benefit to patients. It is necessary to improve research in this area by overcoming barriers such as time needed to perform the studies and obtaining funding. Combined, these efforts could lead to both PRP and BMAC being offered as a standard of care to patients, allowing more to have the opportunity to receive these therapies.
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Appendix 1 – Survey Questionnaire

Introduction to Survey

Subject: Survey of physicians performing point of care regenerative medicine procedures

Dear Colleague,

You have been identified as someone who is currently performing point of care regenerative medicine procedures at your institution or practice. In an effort to better understand perceptions and attitudes of those actively treating patients using these methods, you are being asked for your input. This survey has been developed to help understand the general perceptions of those in the field, methodologies and products used, as well as barriers to moving the field forward.

The survey will take you less than 10 minutes to complete. In order to access, please click on the following:

By completing this survey or questionnaire, you are consenting to be in this research study. Your participation is voluntary and you can stop at any time. Please note that this survey is being done in partial fulfillment of my Master of Science Degree at Johns Hopkins University capstone project. Results may be published but no personal identification will be collected or associated with this survey, nor will the results be used to impact employment. This survey has been approved by both Johns Hopkins’s University and Mayo Clinic Institution Review Boards. If any questions or concerns arise please contact me at bornschlegl.svetlana@mayo.edu.

Thank you for your time,

Svetlana Bornschlegl

Survey Questions:

1. What is your current position at the practice or hospital? Choose 1.
   - Physician
   - Fellow
   - Resident

2. If physician, how many years have you been practicing?
   - 0-5
   - 6-10
   - 10-15
   - 15-20
   - 20+
3. Do you perform BMAC (bone marrow aspirate/concentrate) or PRP (platelet rich plasma) procedures?
   o Yes
   o No
   3.a. If yes, approximately how many per month? (PRP) (BMAC) Choose 1.
       o 1-5
       o 6-10
       o 11-15
       o 15-20
       o 21+

4. What is your instrument of choice for performing BMAC procedures? If you use more than one, please indicate your preferred/primary. Choose 1.
   o Biomet
   o Arthrex
   o EmCyte
   o Other (fill in)

5. Based on your observations in practice, what percent of patients do you believe benefit from these procedures? (PRP) (BMAC)
   o <5%
   o 6-10%
   o 10-25%
   o 25-50%
   o 50-75%
   o 75-100%

6. What is the primary indication for which you use PRP? Choose 1.
   o Orthopedic/Musculoskeletal (non-sports)
   o Autoimmune/Inflammatory
   o Chronic Pain
   o Cosmetic
   o Sports
   o Neurologic

7. What is the primary indication for which you use BMAC? Choose 1.
   o Orthopedic/Musculoskeletal (non-sports)
   o Autoimmune/Inflammatory
   o Chronic Pain
   o Cosmetic
   o Sports
   o Neurologic

8. What is the primary location used with this therapy? (PRP) (BMAC) Choose 1.
   o Knee
9. What is the most common or primary reason this therapy is used? (PRP) (BMAC) Choose 1.
   - Avoid or delay surgery
   - As an analgesic/pain reliever
   - New therapy to treat the disease

10. If you had the freedom to do so, which of the following therapies would you try? Choose 1.
    - Cord blood
    - Amniotic fluid
    - Placental products (other than amniotic fluid and cord blood)
    - Other (fill in)

11. Based on your opinion and/or clinical experience rate the following in the order of safety for patients from 1 (lowest safety) to 9 (highest safety).
    - BMAC (1-9)
    - PRP (1-9)
    - Cord blood (1-9)
    - Amniotic fluid (1-9)
    - Placental products (1-9)
    - Steroids (1-9)
    - Approved biologics (ie Enbrel) (1-9)
    - Surgery (1-9)
    - Joint replacement (1-9)

    - New FDA regulations regarding regenerative treatments will be beneficial to my practice
    - New FDA regulations regarding regenerative treatments will be a burden to my practice and are not necessary

13. Clinics around the US mis-marketing stem cell therapies are driven by? Choose 1.
    - Profit
    - Benefit to patients
    - Patient demand
    - All of the above
    - Other (fill in)
14. Would you suggest BMAC or PRP procedures to a family member or have one performed on yourself?
   - Yes
   - No

15. Do you believe that referring to BMAC procedures without using the terms “stem cells” will deter patients from having the procedure performed at your institution, as they would go elsewhere?
   - Yes
   - No

16. Do you fear that if you do not perform BMAC and PRP procedures that your position or specialty will be jeopardized?
   - Yes
   - No

17. Agree/Disagree: Regenerative medicine procedures are highly beneficial and should be covered by insurance.
   - Agree
   - Disagree

18. What do you believe is the key ingredient in BMAC? Choose 1.
   - Cytokines
   - Platelets
   - WBCs
   - RBCs
   - Stem cells

19. Which values most appropriately reflect the contents of bone marrow? Choose 1.
   - 90% stem cells 10% WBC/RBCs
   - 50% stem cells 50% WBC/RBCs
   - 25% stem cells 75% WBC/RBCs
   - 5% stem cells 95% WBC/RBCs
   - 1% stem cells 99% WBC/RBCs

20. Rate PRP and BMAC technologies on a scale of 1 (low) - 10 (high) on safety and consistency of product across practices. (PRP) (BMAC)
   - Safety (1-10)
   - Consistency (1-10)

21. How do you dose BMAC?
   - Don’t dose
   - Use whatever is produced by the kit
   - Nucleated cell count
22. **How do you dose PRP?**
   - Don’t dose
   - Use whatever is produced by the kit
   - Platelet count
   - Other (fill in)

23. **In your opinion how often can a patient safely have PRP procedures performed?**
    **Choose 1.**
    - No limit
    - Once per month
    - Once every 6 months
    - Once per year
    - Once every 2 years
    - Once every 5 years

24. **How often can a patient safely have BMAC procedures performed?**
    **Choose 1.**
    - No limit
    - Once per month
    - Once every 6 months
    - Once per year
    - Once every 2 years
    - Once every 5 years

25. **Should the FDA regulate PRP?**
    - Yes
    - No

26. **Should the FDA regulate BMAC?**
    - Yes
    - No

27. **Rate your understanding of how instruments used to concentrate BMAC and PRP work.**
    **Choose 1.**
    - Extremely familiar
    - Very familiar
    - Somewhat familiar
    - Not so familiar
    - Not at all familiar

28. **Do companies that distribute these instruments make you aware of improvements made to the machines?**
    - Yes
    - No
28. a. If yes, how well do you understand how these improvements translate into better use of BMAC/PRP?
   - A great deal
   - A lot
   - A modern amount
   - A little
   - Not at all

29. Do you believe the manufacturers of the devices are responsible for demonstrating efficacy and safety of these products?
   - Yes
   - No

30. In your opinion, which statement is most accurate? Choose 1.
   - BMAC/PRP procedures will never become the standard of care.
   - BMAC/PRP will become the standard of care within the next 10 years.
   - Sometime many years in the future they may become a standard of care.

31. In our opinion, what is the most reliable method for measuring patient outcomes? Choose 1.
   - X-ray
   - Ultrasound
   - Clinician evaluation of patient
   - Patient survey/patient reported outcomes

32. What do you find to be the biggest detriment to performing research in this area?
   - Time
   - Financial support
   - Lack of appropriate participants
   - Tracking patients over time
   - Other (fill in)

33. If the outcomes of research performed on the products do not correlate with patient outcomes or are negative, do you believe this will be detrimental to the practice?
   - Yes
   - No

34. Are you aware of prospective, randomized controlled double blind studies showing efficacy of BMAC or PRP?
   - Yes
   - No
35. If a double blind study showed no efficacy but also no adverse events, what would you do? Choose 1.
   o Keep using but wait for more studies to clarify the subgroups it would work
   o Stop using it
   o Use it only if the patient demands it

36. Who should support the ongoing improvement of these technologies? Choose 1.
   o Medical Institutions
   o Companies developing these technologies
   o Government/ Federal Agencies (e.g. NIH, DOD)
   o Private donors
   o Other (fill in)
Appendix 2 – Homewood Institutional Review Board Approval

Homewood Institutional Review Board  
3400 N. Charles Street  
Wyman Park Building, Suite N468  
Baltimore, MD 21218-2685  
410-516-6580  
http://homewoodirb.jhu.edu/  

Michael McClokey, PhD  
IRB Chair

Date: March 27, 2019

PI Name: Marianne Woods  
Study #: HIRB00008802  
Study Name: Attitudes and behaviors among physicians practicing regenerative medicine

Date of Review: 3/26/2019  
Date of Acknowledgement: 3/26/2019  
Expiration Date: 3/26/2022

The above referenced study has been acknowledged.

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No changes may be made to the protocol or the consent form without the approval of the Board.
Appendix 3 – Mayo Clinic Institutional Review Board Approval

Principal Investigator Notification:

From: Mayo Clinic IRB
To: Allan Dietz
CC: Svetlana Bornschlegl
     Allan Dietz
Re: IRB Application #: 19-001650
     Title: Analysis of Attitudes and Behaviors of Physicians Practicing Regenerative Medicine

IRB e Protocol Version: 0.01
IRB e Version Date: 3/5/2019 11:57 AM
IRB Approval Date: 3/11/2019
IRB Expiration Date:

The above referenced application was reviewed by expedited review procedures and is determined to be exempt from the requirement for IRB approval (45 CFR 46.104d, category 2). Continued IRB review of this study is not required as it is currently written. However, any modifications to the study design or procedures must be submitted to the IRB to determine whether the study continues to be exempt.

As protected health information is not being requested from subjects, HIPAA authorization is not required in accordance with 45 CFR 160.103.

AS THE PRINCIPAL INVESTIGATOR OF THIS PROJECT, YOU ARE RESPONSIBLE FOR THE FOLLOWING RELATING TO THIS STUDY.
1) When applicable, use only IRB approved materials which are located under the documents tab of the IRB e workspace. Materials include consent forms, HIPAA, questionnaires, contact letters, advertisements, etc.
2) Submission to the IRB of any modifications to approved research along with any supporting documents for review and approval prior to initiation of the changes.
3) Submission to the IRB of all Unanticipated Problems Involving Risks to Subjects or Others (UPIR/ISO) and major protocol violations/deviations within 5 working days of becoming aware of the occurrence.
4) Compliance with applicable regulations for the protection of human subjects and with Mayo Clinic Institutional Policies.

Mayo Clinic Institutional Reviewer
Curriculum Vitae

Svetlana Bornschlegl works at the Mayo Clinic in Rochester, Minnesota. She oversees and develops new programs in the discovery portion of the IMPACT Lab as well as performs research in cell-based products and therapies. She received her B.S. in Biology and Art from Wisconsin Lutheran College, Milwaukee, Wisconsin, followed by a Master of Science in Research Administration from Johns Hopkins University. In combination she hopes to use this knowledge to advance the research programs at the IMPACT Lab and Mayo Clinic.