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ADVISORY OPINION REGARDING THE USE OF STEM CELL THERAPIES

The Board has observed a significant increase in the number of medical clinics offering stem cell therapy over a relatively short period of time. This increase is consistent with a national trend, but is not necessarily reflective of the efficacy of the treatment. To the contrary, the Board is concerned that some practitioners providing stem cell therapy are not practicing good, evidence-based medicine. Indeed, one need only conduct a Google search for stem cell therapy in South Carolina to find clinics making dubious claims that stem cell therapy is effective therapy for specialties ranging from pain management to orthopedics; from cardiology to neurology; and from wound care to urology. Additionally, the use of stem cells to treat any medical condition is the practice of medicine; however, the Board is aware of some cases where treatment, if not the actual injections, are directed by chiropractors, or other non-physicians (or PAs/APRNs, if appropriate). Furthermore, the Board is concerned that some practitioners are unaware of, or indifferent to, the regulation of this therapy by the FDA. For these reasons, the Board concludes that it is necessary to issue this Advisory Opinion.[1]

1. POTENTIAL FOR HARM

Before analyzing the regulatory framework and setting forth the appropriate standard of care for stem cell therapy, the Board believes it is appropriate to provide a more in-depth review of the potential harm involved in the improper utilization of such therapy. As observed by the Federation of State Medical Boards, "providers and clinics have been known to apply, prescribe or recommend therapies inappropriately, over-promise without sufficient data to support claims, and exploit patients who are often in desperate circumstances and willing to try any proposed therapy as a last resort, even if there is excessive cost or scant evidence of efficacy."[2] Further, the Federation also observed:

[1] S.C. Code Ann. § 40-47-10(I)(1) provides that the Board is authorized to "publish advisory opinions and position statements relating to practice procedures or policies authorized or acquiesced to by any agency, facility, institution, or other organization that employs persons authorized to practice under this chapter to comply with acceptable standards of practice." This Advisory Opinion is intended to provide a broad overview of the Board's position on stem cell therapy. It is not intended to serve as a comprehensive overview of federal law on the subject. The federal regulations governing this issue are nuanced and should be read in context to obtain a full understanding of all possible issues that may arise. Licensees are encouraged to consult private counsel if they have any questions regarding their compliance with federal law.

[2] Federation of State Medical Boards, *Regenerative and Stem Cell Therapy Practices*, April, 2018, https://www.fsmb.org/siteassets/advocacy/policies/fsmb-stem-cell-workgroup-report.pdf. Accessed October 19, 2020.

> Data purportedly supporting unproven stem cell interventions commonly undermine information about risks and overemphasize information about benefits. Treatment options are described on such websites and are often accompanied by supporting information in the form of journal articles, patient testimonials, and accolades related either to the clinic itself or its affiliated physicians and researchers. Supporting information that accompanies marketing materials can appear to be legitimate, but can also overemphasize, exaggerate, inflate, or misrepresent information derived from legitimate (or even questionable) sources.[3]

The FDA has also indicated that it "is concerned that some patients seeking cures and remedies are vulnerable to stem cell treatments that are illegal and potentially harmful."[4]

Indeed, the FDA has identified cases of severe adverse events.[5] For example, one patient became blind due to an injection of stem cells into the eye and another received a spinal cord injection that caused the growth of a spinal tumor.[6] Moreover, the FDA notes that other potential safety concerns for unproven treatments include:

- Administration site reactions;
- The ability of cells to move from placement sites and change into inappropriate cell types or multiply;
- Failure of cells to work as expected; and
- The growth of tumors.[7]

Finally, the FDA notes that even if stem cells are the patient's own cells, there are still safety risks such as those noted above.[8] In addition, if cells are manipulated after removal, there is a risk of contamination of the cells.[9]

Commonly expressed concerns such as those offered by the FSMB and the FDA make clear that the improper utilization of stem cell therapy has the potential to hurt the citizens of South Carolina in their capacities as both consumers and patients. As consumers, individuals, often desperate for treatment, pay significant amounts out-of-pocket for a therapy a practitioner may know offers little, if any, benefit. As patients, individuals undergo treatments where the risks may greatly exceed the potential benefits, if any. For these reasons, it is important that the Board bring attention to, and establish a standard of care for, the utilization of stem cell therapy.

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[3] *Id*.
[4] Food and Drug Administration, *FDA Warns About Stem Cell Therapies*, September 3, 2019, https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies Accessed October 19, 2020.
[5] *Id*.
[6] *Id*.
[7] *Id*.
[8] *Id*.
[9] *Id*.

2. STEM CELLS/HCT/PS

Having discussed the need for this Advisory Opinion, the Board will now provide a brief overview of the FDA's regulatory scheme. The FDA groups stem cells and related products into a category referred to as HCT/Ps, or "human cells, tissues, or cellular or tissue-based products."[10] It defines HCT/Ps as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient" and offers examples including, but not limited to, "bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue."[11]

Further, the FDA considers two forms of use for HCT/Ps: autologous and homologous.[12] "Autologous use" is defined as the "implementation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were recovered."[13] "Homologous use" is defined as the "repair, reconstruction, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor."[14]

As discussed below, HCT/Ps are subject to very different degrees of regulation by the FDA depending on how they are categorized.

3. FEDERAL REGULATION OF HCT/PS

In most cases, HCT/P manufacturers fall into one of two regulatory categories: 1) establishments that manufacture HCT/Ps that are regulated solely under the authority of section 361 of the Public Health Service Act ("PHS Act"); and 2) establishments that manufacture HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act.[15]

a. HCT/PS REGULATED SOLELY UNDER SECTION 361

An HCT/P is regulated solely under section 361 of the PHS Act and accompanying regulations if it meets all of the following criteria:

(1) The HCT/P is minimally manipulated;

[10] 21 C.F.R. § 1271.3(d)
[11] *Id*.
[12] 21 C.F.R. § 1271.3(a) and (c)
[13] 21 C.F.R. § 1271.3(a)
[14] 21 C.F.R. § 1271.3(c)
[15] 21 C.F.R. § 1271.1

(2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

(4) Either:

(i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

(a) Is for autologous use;

(b) Is for allogeneic use in a first-degree or second-degree blood relative; or

(c) Is for reproductive use.[16]

Establishments that manufacture the HCT/Ps described above must: (1) register with FDA; (2) submit to the FDA a list of each HCT/P manufactured; and (3) comply with certain other requirements contained in 21 C.F.R. § 1271.[17] While these requirements for HCT/Ps regulated solely under section 361 may appear complex, they are generally only focused on the prevention of communicable diseases.[18]

b. HCT/Ps that are Regulated as Drugs, Devices, and/or Biological Products under Section 351 of the PHS Act and/or The Federal Food, Drug, and Cosmetic Act

All HCT/Ps other than those described above (subject to minor exceptions) are regulated as drugs, devices, and/or biological products and must comply with Section 351 of the PHS Act and/or The Federal Food, Drug, and Cosmetic Act. These products require pre-market authorization and require clinical investigations under an investigational new drug application and a biologics license through the FDA.[19] As of the date of this Advisory Opinion, the FDA has only approved a small number of HCT/Ps for limited indications. These are primarily umbilical cord-

[16] 21 C.F.R. § 1271.10(a)
[17] 21 C.F.R. § 1271.10(b)
[18] Federation of State Medical Boards, *supra* note 2.
[19] *Id.*

derived stem cell therapies used to treat certain blood cancers and other diseases involving the immune system.[20]

c. A Third Category: Exceptions to the Requirements Contained in 21 CFR Ch. I, Subch. L, Pt. 1271

While most HCT/Ps prompting the issuance of this Advisory Opinion will fall into one of the two categories described above, the FDA has identified limited situations where HCT/Ps are, essentially, unregulated. More specifically, the following are not required to comply with the requirements set forth in 21 CFR Ch. I, Subch. L, Pt. 1271:

(a) an establishment that uses HCT/P's solely for nonclinical scientific or educational purposes.

(b) an establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure.

(c) a carrier who accepts, receives, carries, or delivers HCT/P's in the usual course of business as a carrier.

(d) an establishment that does not recover, screen, test, process, label, package, or distribute, but only receives or stores HCT/P's solely for implantation, transplantation, infusion, or transfer within its facility.

(e) an establishment that only recovers reproductive cells or tissue and immediately transfers them into a sexually intimate partner of the cell or tissue donor.

(f) an individual under contract, agreement, or other arrangement with a registered establishment and engaged solely in recovering cells or tissues and sending the recovered cells or tissues to the registered establishment is not required to register or list HCT/Ps independently, but must comply with all other applicable requirements in this part.[21]

4. Impact of FDA Regulatory Categories on Practitioners

The FDA's regulatory scheme for HCT/Ps results in a limited set of circumstances in which manufacturers may produce, and by extension, practitioners may utilize, HCT/Ps. Unless a practitioner is participating in a clinical trial or otherwise meets an exception, a practitioner may only utilize an FDA-approved HCT/P, unless the HCT/P is regulated solely under section 361 of

[20] Pew Charitable Trust, *FDA's Framework for Regulating Regenerative Medicine Will Improve Oversight*, October 17, 2019, https://www.pewtrusts.org/en/research-and-analysis/reports/2019/10/17/fdas-framework-for-regulating-regenerative-medicine-will-improve-oversight. Accessed October 19, 2020. The full list of approved products is available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products.

[21] 21 C.F.R. § 1271.15

the PHS Act. Utilizing a non-approved HCT/P is no different that prescribing a drug that has not been approved by the FDA. As mentioned above, as of the date of this Advisory Opinion, the FDA has only approved a small number of HCT/Ps for limited indications. These are primarily umbilical cord-derived stem cell therapies used to treat certain blood cancers and other diseases involving the immune system.[22]

5. REMAINING USES OF HCT/PS

Subject to the above, practitioners are limited to utilizing HCT/Ps that are regulated solely under section 361 of the PHS Act or otherwise exempted from regulation. The utilization of these HCT/Ps are subject to the basic principles of good medical care. In April of 2018, the Federation of State Medical Boards issued a policy on Regenerative and Stem Cell Therapy Practices.[23] In its policy, the Federation offered certain recommendations for the utilization of HCT/Ps, including the following:

- Where evidence is unavailable for a particular treatment in the form of clinical trials or case studies, physicians must only proceed with an appropriate rationale for the proposed treatment, and justification of its use, in relation to the patient's symptoms or condition. Novel, experimental, and unproven interventions should only be proposed when traditional or accepted proven treatment modalities have been exhausted. In such instances, there must still be a basis in theory or peer-acknowledged practice.

- As with all medical treatment, the physician must obtain informed consent for the use of HCT/Ps from the patient. The process of obtaining such informed consent should include the following elements, at a minimum:

    - An explanation, discussion, and comparison of treatment options with the patient;

    - An assessment of the patient's values and preferences;

    - Arrival at a decision in partnership with the patient; and

    - An evaluation of the patient's decision in partnership with the patient.

- Physicians must only offer treatments to patients for which they have a bona fide physician/patient relationship. Physicians must have received adequate and appropriate training, and be able to perform any proposed intervention safely and competently.

[22] Pew Charitable Trust, *supra* note 12. Further, a warning about stem cell therapies issued by the FDA on September 3, 2019 provides that the only stem cell-based products that are FDA-approved for use in the United States consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood. These products are approved for limited use in patients with disorders that affect the body system that is involved in the production of blood (called the "hematopoietic" system). Food and Drug Administration, *supra* note 4.

[23] Federation of State Medical Boards, *supra* note 2.

- Physicians must avoid any claims that may be deceptive or are intentionally or knowingly false or misleading, especially in terms of making promises about uncertain or unrealistic outcomes.

- Physicians should be prepared to support any claims made about benefits of treatments or devices with documented evidence, for example with studies published in peer-reviewed publications.

- Physicians should consult and educate patients about stem cell interventions and alert them to important resources available to the community.

The Board believes that these well-reasoned recommendations accurately reflect the standard of care for the utilization of HCT/Ps and adopts them as the applicable standard of care in South Carolina.

In addition to the principles set forth above, physicians utilizing HCT/Ps should:

- Exhaust all FDA-approved procedures/treatment prior to utilizing non-approved procedures/treatment;

- Maintain appropriate records of the treatment, including 1) the indication(s) for the treatment; 2) alternative treatments that were tried and/or considered prior to the utilization of HCT/Ps; 3) documentation of the procedure, including any adverse events; and 4) documentation of follow-up visit(s);

- Conduct a follow-up evaluation of the patient as appropriate;

- Have received appropriate training and education regarding the use of HCT/Ps. Such education and training should be reflective of the fact that treatment involving HCT/Ps is mostly unproven and, as such, a physician will require education and training beyond that required for the utilization of commonly-accepted, proven treatments. Individuals should have a fundamental understanding of theory and peer-acknowledged practices and should engage in continued study of HCT/Ps;

- Must, as part of their education and training, know of, understand, and be able to recognize all possible contraindications. Physicians must obtain a medical history and perform a complete physical examination of the patient prior to utilizing HCT/Ps;

- Recognize that the physician is ultimately responsible for the continued care of patients who receive injections of HCT/Ps. The physician is responsible whether he/she performs the injection, or whether it is performed by a PA or APRN. A physician may only delegate (or authorize in a Collaborative Practice Agreement or Scope of Practice Guidelines) the injection of HCT/Ps to a PA and/or APRN with the appropriate education and training as described above. The physician, and other members of the health care delivery team, are responsible for the continued care of patients related to the condition for which they received HCT/Ps;

- Must, in addition to the requirements for informed consent contained in the FSMB recommendations set forth above, as adopted by the Board, explain all likely outcomes of treatment utilizing HCT/Ps based on established medical evidence. The patient must be informed of the risks, benefits, and alternatives to the use of HCT/Ps. The patient's chart must include documentation that that this information was discussed with the patient and that the patient understands and agrees to the use of HCTP/Ps. Finally, as part of obtaining informed consent, the Physician must address whether the HCT/Ps recommended are FDA-approved or experimental. If administered off-label, the patient must be informed that the use of HCT/Ps has not been approved for treatment of the patient's condition; and

- Not delegate the injection of any non-FDA-approved HCTPs to any personnel; APRNs and/or PAs may, however, administer FDA-approved HCTPs as indicated if such act is included in their Collaborative Practice Agreements and/or Scopes of Practice Guidelines.

The Board believes that these additional recommendations, along with the FSMB recommendations set forth above, accurately reflect the standard of care for the utilization of HCT/Ps and adopts them as the applicable standard of care in South Carolina.
