The Problem: **Islet allotransplantation (allo-ITx) in the United States (US) is facing an imminent demise, leaving patients with type 1 diabetes mellitus (T1DM) and severe hypoglycemia without access to a lifesaving therapeutic procedure**

The safety and effectiveness of allo-ITx has been established in NIH-sponsored US clinical trials as well as through the Collaborative Islet Transplantation Registry- US taxpayer-funded research projects, which collectively have analyzed data from more than 2,000 allo-ITx procedures over the past 20 years.

However, despite decades of progress in the field driven by US academic centers, an archaic regulatory framework has stymied US clinical practice. Current Food and Drug Administration (FDA) requirements for allogeneic islets for transplantation do not reflect the clinical or technical state-of-the-art.

- Autologous islets (*auto*-islets) and **allogenic islets** (*allo*-islets) are sourced and processed identically, but are subject to vastly different FDA regulatory requirements:
    - *Auto*-islets, like many tissue- and cellular-based products, are subject to limited requirements aimed at ensuring appropriate collection, storage, processing, and distribution (**Section 361** Public Health Service (PHS) Act).
    - *Allo*-islets, in contrast, are subject to much more extensive requirements because they are categorized as biological drug (**section 351** PHS Act and Federal Food, Drug and Cosmetics Act).
- The distinction between *auto*- and *allo*-islets based on criteria established nearly 30 years ago (21 CFR Part 1271), which do NOT reflect current standards and clinical practice. But, the significant burden placed on *allo*-islets has effectively prevented their therapeutic use in the US:
    - In the past four years, only 11 new patients have undergone allogenic islet transplantation (allo-ITx) in the US, all under an investigational protocol. **In contrast, in** Europe, Canada, Australia, and Japan, **islets are NOT regulated as a drug** and allo-ITx is a **standard-of-care procedure** annually benefits hundreds of patients with type 1 diabetes.
- *Allo*-islets in the US require premarket approval of a biologics license application (BLA) and extensive post-market compliance obligations. FDA's requirements are geared to commercial manufacturers of drug products, and not to clinical transplant centers. Only a commercial (pharma/biotech) company realistically could comply with these requirements. Regulating transplant centers as drug manufacturers and requiring premarket approval for *allo*-islets therefore effectively precludes clinical transplant centers from offering allo-ITx to patients, while not improving patient safety.

- The first commercial entity to obtain FDA approval of a BLA for *allo*-islets will be eligible for seven years of market exclusivity, further limiting patient access to the therapy. The price for FDA-approved *allo*-islets produced by a commercial manufacturer foreseeably will be significantly inflated due to need to recover enormous cost of preparing a BLA and complying with the manufacturing regulations for commercial drugs. The absence of competition, at least initially, foreseeably will also escalate the price and discourage innovations in islet processing, to the detriment of patients who could benefit from this life-saving therapy.
- Allowing the commodification of islets runs counter to the ethical norms underlying the organ and tissue transplantation framework, under which the sale of organs and tissues is prohibited, and organ donation is viewed as an altruistic act.

The Solution:

We propose to harmonize the US approach to *allo*-ITx with that of many other countries, which would allow for implementation of safe, effective, affordable, and widely accessible islets for transplantation as a standard of care procedure.

- **Specifically, we seek r**econsideration of the FDA regulatory status of *allo*-islets on an expedited basis, before a BLA is issued and orphan designation is awarded to a single commercial sponsor (which could happen as soon as March 2021).
- *Allo*-islet regulation should be consistent with the regulation of *auto*-islets and other **minimally-manipulated human tissue for transplantation.**

We recommend that FDA:

1. Confirm that islet *allo*-islets are "minimally manipulated" Human Cells, Tissues, Cellular and Tissue-Based Products (HCT/Ps) as that term is defined in FDA regulations, because they are subject to only short-term incubation prior to *allo*-islet infusion that does not alter their relevant biological characteristics.,
2. Allow allogeneic islets from unrelated donors to be eligible for regulation as HCT/Ps exclusively under Section 361/Part 1271, provided that donors and recipients are immunologically compatible as determined by current clinical standards for immunological matching in organ and cell/tissue transplantation.

We recommend that HRSA, through UNOS/OPTN, continue to oversee pancreas allocation and procurement and extend its oversights of transplant programs to include those that perform islet transplantation, which would allow HRSA to monitor the outcomes of patients receiving allo-ITx.

Conclusion: *Allo*-islets is a "poster child" for archaic over-regulation. Adjusting the regulation would remove regulatory barriers, reflect our current clinical practice and to deal with upcoming challenge. Propose updates to current regulations are critical for the renaissance of ethical, safe, effective, and affordable allo-ITx in the United States.