Islets for US Collaborative

Pancreatic Islet Transplantation for Patients with Type 1 Diabetes in the US
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The Demise of Islet Allotransplantation in the US: A Call for an Urgent Regulatory Update
Urgent need for a regulatory update.

The "Islets for US" Collaborative

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Abbreviations:

allo-islets- allogeneic islets, islet allograft
allo-ITx – pancreatic islet allotransplantation
BLA- Biologics License Application
CITC- Clinical Islet Transplantation Consortium
CFR- Code of Federal Regulations
CMS- Centers for Medicare and Medicaid Services
FDA- Food and Drug Administration
GMP - Good Manufacturing Practice

cGMP- current Good Manufacturing Practice
JDRF- Juvenile Diabetes Research Foundation
HLA – Human Leukocyte Antigen
HRSA- Human Resources Services and Administration
HCT/Ps - human cell and tissue products
NIH- National Institutes of Health
ODD – Orphan Drug Designation
OPTN- Organ Procurement and Transplantation Network
PHS- Public Health Service
SHE- Severe Hypoglycemic Episodes
SRTR- Scientific Registry of Transplant Recipients
T1DM- Type 1 Diabetes Mellitus
UNOS- United Network for Organ Sharing

Abstract

Islet allotransplantation in the United States (US) is facing an imminent demise. Despite nearly three decades of progress in the field, an archaic regulatory framework has stymied US clinical practice. Current regulations do not reflect the clinical or technical state-of-the-art.

Whereas many human cells, tissues, and cellular and tissue-related products (HCT/Ps) are eligible for limited oversight aimed at ensuring appropriate screening, collection, storage and handling practices, the Food and Drug Administration (FDA) regulates islet allografts as biological products. This regulatory distinction impedes patient access to human islets for transplantation. As a result, only 11 patients have undergone allogenic islet transplantation (allo-ITx) in the US within the last 4 years, whereas in other countries, this standard-of-care procedure annually benefits hundreds of patients with type 1 diabetes.

Herein, we describe the current regulations pertaining to islet transplantation in the US. We explore the progress which has been made in the field and demonstrate why the regulatory framework must be updated to both better reflect our current clinical practice and to deal with upcoming challenges. We propose specific updates to current regulations which are required for the renaissance of ethical, safe, effective, and affordable allo-ITx in the US.

Introduction

Human islets are considered as tissue for transplantation in many countries, which has contributed to allogeneic islet transplantation (allo-ITx) becoming a standard-of-care procedure for select patients with type 1 diabetes mellitus (T1DM) (Table S1B).[1] In contrast, in the United States (US), human islets have been regulated as biological products and therefore subject to FDA premarket approval and other requirements (Table 1;1-3,9,16,17). A sponsor seeking to perform allo-ITx in a clinical setting must first obtain FDA approval of a biologics license application (BLA), and must demonstrate, through both non-clinical and clinical studies, that the cells are "safe, pure, and potent" (i.e. safe and effective) for their intended use. Sponsors must also demonstrate that the products are manufactured in accordance with current good manufacturing practices (cGMP) applicable to biological products (Table 1;2,3,9,11,12,15).

Due to this heavy regulatory burden and the associated financial, administrative, and logistical hurdles, no allogeneic islets have been approved by the FDA to date, and allo-ITx has been available only investigationally in the setting of clinical trials.[1,2] As a result, only one sponsor, a commercial entity, has to date submitted a BLA for allo-ITx, for the treatment of "brittle" T1DM. Furthermore, since all biological products, unlike many HCT/Ps, are eligible for market exclusivity under the Orphan Drug Act, should the FDA grant this sponsor's BLA, no other sponsor would be able to obtain premarket approval for allo-ITx for brittle T1DM for a period of seven years (Table 1;4-6).

Herein, we report on the current status of allo-ITx and provide an overview of existing regulations vis-à-vis the advances in scientific knowledge and clinical practice of the past 27 years. We call for an urgent update of an outdated regulatory framework to ensure that islet allografts remain a public resource for transplantation in the US. We propose that islet allografts should be regulated **solely** under Section 361 of the Public Health Service Act and the corresponding HCT/P regulations in Part 1271 of Title 21 of the Code of Federal Regulations. We also suggest additional clinical oversight using the same framework as for organ transplantation.

Regulations related to allo-ITx in the US

The FDA's statutory authority derives principally from the Federal Food, Drug, and Cosmetic (FD&C) Act which pertains to "drugs" and the Public Health Service (PHS) Act, which concerns the regulation of "biological products" via Section 351 and gives the agency authority to implement requirements for control of communicable diseases via Section 361 (Table 1;1-3).

For decades, the FDA, with few exceptions, did not regulate human tissues used in transplantation. However, concerns about the transmission of HIV in the 1990s prompted re-examination of this policy. The FDA therefore enacted regulations, pursuant to Section 361 of the PHS Act, like donor screening and record keeping, to ensure the safety and integrity of tissues used in transplantation (Table 1;1,2).

Concurrently, the FDA began to recognize that human cells and tissues were being investigated for novel uses beyond their traditional applications, which prompted consideration whether they should be subject to regulation under the FDA's drug and biologics authorities. After a decade of deliberation, the Code of Federal Regulations Part 1271 was enacted and established the criteria by which the FDA would determine whether an HCT/P would be regulated solely under Section 361 of the PHS Act or would be additionally regulated as a drug, biological product, or medical device (or some combination thereof) under Section 351 of the PHS Act and the relevant sections of the FD&C Act (Table 1;2).

In order to be regulated solely under Part 1271, the HCT/P must be (1) "minimally manipulated," and (2) intended for "homologous use." In addition, if the HCT/P in question has a "systemic effect" or is "dependent on the metabolic activity of living cells for its primary function" then it must be limited to (i) autologous use, (ii) allogeneic use in a first or second degree blood relative, or (iii) reproductive use. Allogeneic islets considered as HCT/P with systemic effect that does not meet these criteria, have been subject to the FDA's regulation as a drug, biological product, and/or medical device.

Additionally, FDA considered allogeneic islets as "more than minimally manipulated" because they are placed in culture media after extraction from the donor pancreas (Table 1;13,14). Consequently, even though these islets are not altered from their native state and are intended to perform the identical function in the recipient as they did in the donor, their therapeutic use is not permitted unless they comply with the premarket and postmarket requirements applicable to biological products. Requirements include pre-clinical and clinical testing, preparation and submission of a BLA, and implementation of all necessary standards during production, distribution, and marketing.[3] The regulatory burden is progressive, with costs increasing dramatically as phases of development are completed.[4] Even academic medical institutions with well-established organ transplantation programs are unlikely to have the resources to satisfy many of these requirements.

In contrast, *autologous* and related-allogeneic islets are regulated as HCT/Ps solely under 361 PHS Act and 21 CFR Part 1271 and not as a biological product. Notably, related-allogenic islets are practically not performed due to the risk to the living donor. Both autologous and related-allogenic islets have a systemic effect on the body (i.e. production of insulin). Furthermore, both are isolated using the same processing protocol, technology, materials, and facilities as unrelated allogenic islets[5]. However, notwithstanding these similarities, non-related allogeneic islets are categorically ineligible for regulation solely under Part 1271. Additionally, while autologous islets are infused into the patient immediately following isolation, allogenic islets are preserved in culture media prior to infusion[5]. Since FDA takes the position that "cell culture generally alters the relevant biological characteristics of cells or tissue" (Table 1;13,14), the FDA appears to presume that allo-ITx are "more than minimally manipulated." Consequently, allo-ITx are subject to more restrictive regulation as a biological and drug product. (Table 1;13,14).

While historically, allogeneic islets were cultured for several days to limit acinar tissue in the islet preparation before transplantation, this practice was replaced by routine mechanical islet purification 20 years ago.[6,7] For example, "fresh" (i.e. uncultured) islet infusions were utilized in a multicenter phase 1/2 clinical trial in the US (2001-2005).[7] In subsequent clinical trials, islets were maintained for up to 72 hours prior to infusion for logistical reasons (e.g. pre-operative patient preparation).[8–11] Since islets, similarly to whole organs, but in contrast to stem cells, cannot be stored frozen, they were placed in an incubator with the goal of preservation only (i.e. to maintain their biological structure and function).[9,10] The medium used for islet preservation has no growth factors and contains only supplements permitted by the FDA for minimally-manipulated cells (Table 1;7).[9] Extensive validation studies performed during the NIH-supported Clinical Islet Transplantation Consortium (CITC) trial confirmed that short (up to 72 hours) incubation for the purpose of storage only **did not alter the relevant biological characteristics of human islets** and that function remained preserved until infusion.[9,10] Therefore, short-term incubation of islet allografts meets the criteria for HCT/P storage/preservation and islets should NOT be considered as "more than minimally manipulated" under Part 1271 (Table 1:7).

Furthermore, the regulatory distinction between autologous/related islets and allo-ITx is no longer justified. Over 20 years ago, when these regulations were conceived, clinical outcomes were indeed better in patients who received cells, tissues, and organs from first and second-degree relatives than in those who received transplants from unrelated donors. Currently, we no longer rely on biological relationships but instead use appropriate immunological matching. In fact, the risk of immunologic sensitization among first-degree relatives might be higher in the case of exposure of the mother to human leukocyte antigens (HLA)s from the child or father during pregnancy and delivery. Thus, the safety and efficacy of both related and unrelated allogeneic transplants are ensured by immunological matching/compatibility using donor and recipient HLA blood and tissue typing. In the current era, the safety and efficacy of related and unrelated but appropriately matched donor/recipient pairs are comparable.[12,13] Additionally, rules of immunological matching might differ among various HCT/P therapies and treated diseases. For example, in type 1 diabetes mellitus (T1DM) we avoid HLA matching due to an increased risk of recurrent autoimmunity.[14] Therefore, the categorical exclusion of non-related allo-ITx from regulation as an HCT/P solely under Part 1271 is outdated. Unrelated allo-ITx should no longer be regulated differently from related allo-ITx given the advanced immunological matching algorithms currently used in clinical practice.

Allo-ITx experience in the US

Transformative progress in allo-ITx was achieved in 2000, when a series of seven patients with T1DM remained insulin-free for one year post-procedure.[6] At that time, the FDA confirmed that islet allografts needed to be regulated as a biological product and subject to

investigational new drug (IND) testing requirements prior to marketing (Table 1;15,16). Federally funded clinical trials were conducted over a span of the next 15 years and involved several US academic centers with a total expenditure of over $100M (Table S1;A). The results achieved by this collaborative endeavor have played a crucial role in the establishment of allo-ITx worldwide, but oddly, not in the US.

Despite proven safety and efficacy, the adoption of allo-ITx has been deterred by US regulatory constraints.[2] The sponsor of a BLA for an allogeneic islet product must comply with extensive regulatory requirements which apply to new biological products.[3,4] The cost of preparing a BLA submission alone is $5-6 million; substantial additional costs and regulatory requirements arise from postmarket obligations and liabilities.[2] Consequently, none of the academic medical centers comprising the Clinical Islet Transplantation Consortium, which led the US clinical trials that demonstrated the safety and efficacy of allo-ITx for T1DM, have the resources and capacity to submit a BLA, and therefore are unable to offer therapeutic allo-ITx to patients who could benefit from them.[2,3]

Consequences of the current regulations on the status of allo-ITx in the US

1) **Near extinction of islet transplantation in the US**

   To date, no BLA has been approved; therefore, no islets have been transplanted outside of clinical trials and the procedure is not generally reimbursed by medical insurers in the US. Limited research funding, as well as the high cost of performing the procedure (>$138,000), are inherent constraints on the investigational availability of allo-ITx.[15] In the US, only 11 new patients received an allo-ITx in the past four years, in contrast to 179 islet transplants performed as part of clinical investigations between 1999-2005 (Figure 1).

2) **No access for Americans with severe hypoglycemia to a lifesaving procedure**

   Among the 1.2 million Americans with T1DM, approximately 375,000 suffer from impaired hypoglycemic awareness and 66% suffer from recurrent severe hypoglycemic episodes (SHE).[16,17] Most importantly, nearly 70,000 T1DM patients fail to improve despite structured education and advanced technologies for hypoglycemia avoidance.[16-18] Quality of life for these patients and their families is severely compromised by sudden and unexpected episodes of loss of consciousness, frequently leading to disability and fatal accidents. Additionally, anxiety and depression are related to an increased risk of death secondary to unrecognized hypoglycemia.[19] Despite significant improvements in insulin pumps and continuous glucose monitoring sensors, hypoglycemic episodes have remained a significant hurdle for patients with T1DM in the US leading to an estimated 40,000 annual visits to emergency departments.[19,20] Overall mortality rates remain at 4% for medically optimized patients in contrast to no deaths in those who underwent islet transplantation.[21,22] Pancreas transplantation remains an approved therapeutic option effectively

treating diabetes in this subset of patients. However, it requires major surgery with a 10-20% risk of operative complications.[23]

Allo-ITx is a minimally-invasive alternative, particularly for patients who are not candidates for surgery; it has lower morbidity and mortality, improved glycemic control and prevention of SHE, even when additional procedures are required to maintain long-term insulin independence (Table S1).[23,24] Allo-ITx should be avoided in patients with chronic kidney disease to limit immunologic sensitization prior to kidney transplantation, unless part of a simultaneous islet-kidney or islet following kidney transplantation. Lastly, islet and pancreas transplantation require continuous administration of immunosuppression. Other modern cellular therapies (e.g. encapsulated pluripotent stem cell derived islet transplantation and xenotransplantation) have been tested clinically but are still under development.

3) Islet allografts are not regulated as biological products and are routinely transplanted in many developed countries

Islet processing technology initially developed in the US has been freely adopted worldwide. Results from US clinical trials prompted regulatory agencies in other countries to recognize, in contrast to the FDA, that the biological characteristics of islet allografts do NOT change during processing and preservation/incubation prior to transplantation (Table 1;19).[1] Therefore, in Europe, islets are NOT regulated as "advanced therapy medicinal products" (i.e. the equivalent of biologic products in US) and have not been subject to marketing authorization requirements. Many other countries have a similar regulatory framework (Figure 2). Nevertheless, to provide the appropriate environment and monitoring, islets are still processed in special laboratories (i.e. GMP facilities) designed for aseptic cell product processing and which implement pertinent standards borrowed from the Good Manufacture Practice (GMP) (Table 1;20).[25] After islet preparation, the allo-ITx procedure is performed in accredited transplant centers and together this leads to excellent clinical safety and efficacy outcomes worldwide (Table S1;C).[21,26,27] Remarkably, islets have been processed and transplanted in the US under the same conditions (i.e. in a facility meeting cGMP standards but without the full implementation of cGMP regulatory requirements for biological product manufacturing) but only under an IND. In the most experienced programs, five-year insulin independence rates are ~ 50% and more importantly, allo-ITx confers complete protection from SHE in ≥ 90% of patients (Table S1;D).[26,28] Notably, other countries ensure access to human islets by limiting commercialization and providing financial support for programs by national health systems (Figure 2B, Table S1;B).[1]

In 2019, the American Society of Transplantation's Board of Directors and the Council of the American Society of Transplant Surgeons called upon the FDA to address these needed changes in islet allograft regulation. A comprehensive proposal including the data and rationale presented in this article was submitted and presented to the FDA in February 2020. However, the FDA has not pursued any updates to its regulations (Table 1;7).

Recommendations for an updated regulatory framework for islet allografts

Our proposal calls for a regulatory update in line with current scientific knowledge and standards of clinical practice. We propose the implementation of combined oversight of islet transplantation with the FDA regulating islet processing solely under Part 1271 of HCT/P regulations and the Organ Procurement and Transplantation Network (OPTN)/ United Network for Organ Sharing (UNOS) overseeing clinical islet transplantation (Figure 2A).

1. **Update current FDA regulations**

We urge the FDA to update current regulations and allow islet **allo**grafts to be eligible for regulation solely under Part 1271, to the same extent as islet **auto**grafts (Table 1;3,7).

Specifically, we recommend that the FDA:

A) Confirm that islet allografts, being subject to short-term incubation that does not alter their relevant biological characteristics prior to allograft infusion, are "minimally manipulated" HCT/Ps as that term is defined in FDA regulations.

B) Allow unrelated allogeneic islets to be eligible for regulation as HCT/Ps exclusively under Section 361, when donors and recipients are immunologically compatible as determined by current clinical standards for immunological matching in organ and cell/tissue transplantation.

Revising the HCT/P regulations would be consistent with the FDA's recognition, from the inception of the regulatory paradigm for cell and tissue therapies, that these regulations might need to be modified over time in light of new knowledge and clinical experience.[3] Consequently, we should re-assess and update allo-ITx regulations in accordance with currently available science and clinical practice.

2. **Introduce additional clinical oversight by OPTN/UNOS**

Another consequence of the current FDA regulation of allo-islets as a biological product is that, following BLA approval, program accreditation from OPTN/UNOS would not be required in order to perform allo-ITx, nor would OPTN/UNOS necessarily monitor clinical outcomes, as it does for all solid organ transplants. However, allo-ITx involves risks of immunosuppression, transmission of infections, and allo-sensitization that are similar to solid organ transplants.

Thus, the care of these patients demands a highly specialized, multidisciplinary approach with properly structured medical and social support to achieve optimal clinical outcomes. Lack of clinical oversight, of the type that would be provided by OPTN/UNOS, may lead to inadequate monitoring and data tracking, and inferior outcomes. Furthermore, islet allograft anatomy, physiology, and preservation techniques more closely resemble those of other human organs rather than any drug or single cell biologics (Figure S1). Similar to other solid organ transplantation, monitoring post-procedural outcomes following allo-ITx undoubtedly is a better means to assess the quality of donor tissue after processing than any pre-transplant *in vitro* testing. Therefore, adherence to BLA standards for allo-ITx is conceptually flawed and should be replaced by close post-transplant outcome monitoring by OPTN/UNOS (Figure 2, Table 1;21-24).[28,29]

What will happen if we do NOT update the current regulations?

Since not-for-profit organizations have not been able to offset the burden, liability, and costs related to BLA, only a for-profit entity with appropriate resources can adhere to the current islet regulatory framework mandated by the FDA. However, this scenario is unlikely to expand access to safe, affordable, and equitable allo-ITx.

When regulated as a biological product, allo-ITx for T1DM and complicated hypoglycemia is eligible for orphan drug designation (ODD) and market exclusivity, since the condition affects fewer than 200,000 people in the U.S (Table 1;4,6). The FDA has granted numerous ODDs for islets for brittle T1DM (Table 1;5); the first applicant to obtain a BLA will receive market exclusivity, and no other sponsor will thereafter be able to obtain FDA approval for a period of seven years (Table 1;4,15). Currently, only one recipient of an ODD, the for-profit company CellTrans, has submitted a BLA to the FDA; we understand that the user-fee goal date for an action on the submission, which was submitted in May 2020, is April 2021 (personal communication; Dr. José Oberholzer, Aug. 20, 2020). This creates an imminent ethical and legal dilemma in which a private company may have exclusive rights to benefit from altruistic human organ donation. This possibility would undermine the public goods concept of organ donation and may undermine the public's trust in the national organ donation system. Prevention of islet commercialization was one of the reasons cited by the European Union in its decision to exclude islets from regulation as a biologic (Table 1;19).[1]

Although a sponsor may choose to waive exclusivity, assurances of a waiver of exclusivity are insufficient given the commercial pressure generated by the enormous costs of preparing a BLA submission and manufacturing allo-ITx in accordance with the standards required for biological products. Cost of allo-ITx may increase substantially following BLA approval and market exclusivity and this will translate to a less affordable, and possibly even cost-prohibitive, option for many patients. If only private payors provide reimbursement coverage, and the Centers for Medicare and Medicaid Services (CMS) or state Medicaid programs do not, this may disproportionately disadvantage patients of low socio-economic status. Even if CellTrans were to waive the exclusivity rights, the extreme cost and burden

related to BLA submission (e.g. 100,000 pages of documents, reports of 1.5 million data points) [personal communication; Dr. José Oberholzer, Aug. 20, 2020] and the cost and burden of operations afterwards in a relatively small market may effectively discourage any potential competitors.

Furthermore, uncontrolled distribution of islet products without any clinical surveillance system in place may lead to poor clinical outcomes and hinder advances in clinical management. Typical postmarketing FDA oversight based only on voluntarily reporting of adverse events to the manufacturer is insufficient to monitor postmarket safety of allo-ITx.

What will happen if the recommended regulatory updates for allo-ITx are enacted?

We anticipate several positive impacts of the proposed regulatory updates (Table S2): 1) The human pancreas and isolated islets will be protected from market exclusivity and unconstrained commercialization and remain a public resource as in other countries. The center transplanting a patient will be ultimately responsible for clinical outcomes and may choose to process the islets in its own cGMP facility or to outsource that service. Competition among institutions would lead to direct quality improvements and price regulation. 2) BLA-related regulatory barriers will be removed, allowing allo-ITx to become a standard-of-care procedure as recommended by experts and professional societies. 3) Payors can be approached for reimbursement of a non-investigational procedure. 4) Not-for-profit academic centers will be able to process islets, providing safe and cost-effective treatments. 5) Clinical oversight from OPTN/UNOS will help optimize clinical outcomes. 6) The number of islet isolation centers will increase, and competition will drive improvements in quality, cost-effectiveness, and patient access. 7) As the cost of the procedure declines, it will be more affordable and comparable to pancreas transplantation even if repeat allo-ITx procedures are required. 8) Significant allo-ITx clinical activity will reinvigorate research. Advances in islet transplantation will stimulate progress in regenerative medicine, cellular therapies, and organ bioengineering. Ultimately, this would benefit our patients and strengthen diabetic care.

Additional safety and quality considerations

If regulations are updated, we anticipate that: 1) high standards of allo-ITx will be reinforced by OPTN/UNOS via program accreditation and transparent surveillance of outcomes (Table 1;21-24). Similar to pancreas transplant programs, outcome measures including waitlist mortality rates, transplantation rates, and 1-year and 3-year patient and graft survival rates, will be monitored by the OPTN and publicly reported by the Scientific Registry of Transplant Recipients (SRTR) on a bi-annual basis. The OPTN Pancreas and Islet Transplantation Committee remain vigilant and regularly update polices and bylaws to ensure safety and efficacy. Islet graft failure criteria can be adopted from experts' consensus.[30] 2) Islets would be regulated solely under Part 1271 and require compliance with current Good Tissue Practice (cGTP)

requirements. However, the FDA could enhance cGTP requirements as needed to address specific issues related to allo-ITx, for example, by mandating islet processing in a proper "clean room" facility. There is precedent for this approach; in the FDA's cGTP guidance, the agency suggests that cGTP facilities take into account cGMP guidance in determining appropriate environmental controls (Table 1;8). Once regulations are updated, the FDA could issue new guidance specifically for human islet processing identifying critical elements and standards for aseptic HCT/P processing which would be a prerequisite for OPTN program accreditation (Table 1;9). Each islet processing facility would also be subject to FDA registration, certification, and unannounced visits/inspection as a tool to ensure safety and reinforce compliance with regulations. The BLA requirement is designed for any new drug entering an open market without any outcome control measures; however, under the proposed regulatory framework, the BLA requirement will become obsolete as human islets will be overseen by the dual surveillance systems of OPTN/UNOS and specifically defined FDA cGTP control. Additionally, ample scientific evidence from over 2,000 procedures worldwide, collected by the NIH sponsored CITR (including US clinical trial data), sufficiently justifies the addition of allo-ITx to the list of other HCT/Ps exempt from BLA without any compromise in safety or outcomes.[10,28,29] The OPTN could set expected outcomes initially at the level of a phase 3 CITC trial with the same product release criteria and clinical indications. Programs will need to comply with requirements to obtain and maintain accreditation for allo-ITx and will need to demonstrate capability and records. Experienced centers will drive clinical excellence while underperforming centers will be directed to make improvements supervised by the OPTN Membership and Professional Standards Committee, and if unsuccessful may lose OPTN accreditation and contracts for reimbursement.

Summary

Urgent regulatory updates that incorporate current clinical standards and research findings are indispensable for the re-introduction of ethical, safe, effective and affordable allo-ITx in the United States. We argue that islet allografts are minimally-manipulated HCT/Ps and propose that FDA revise its regulations to permit appropriately-matched islet allografts to be regulated solely under Part 1271 of the Code of Federal Regulations. We call for additional clinical oversight for allo-ITx using the same framework as for organ transplantation. The US Department of Health and Human Services should promote these changes to improve and protect the public's health and to strengthen the US health system.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

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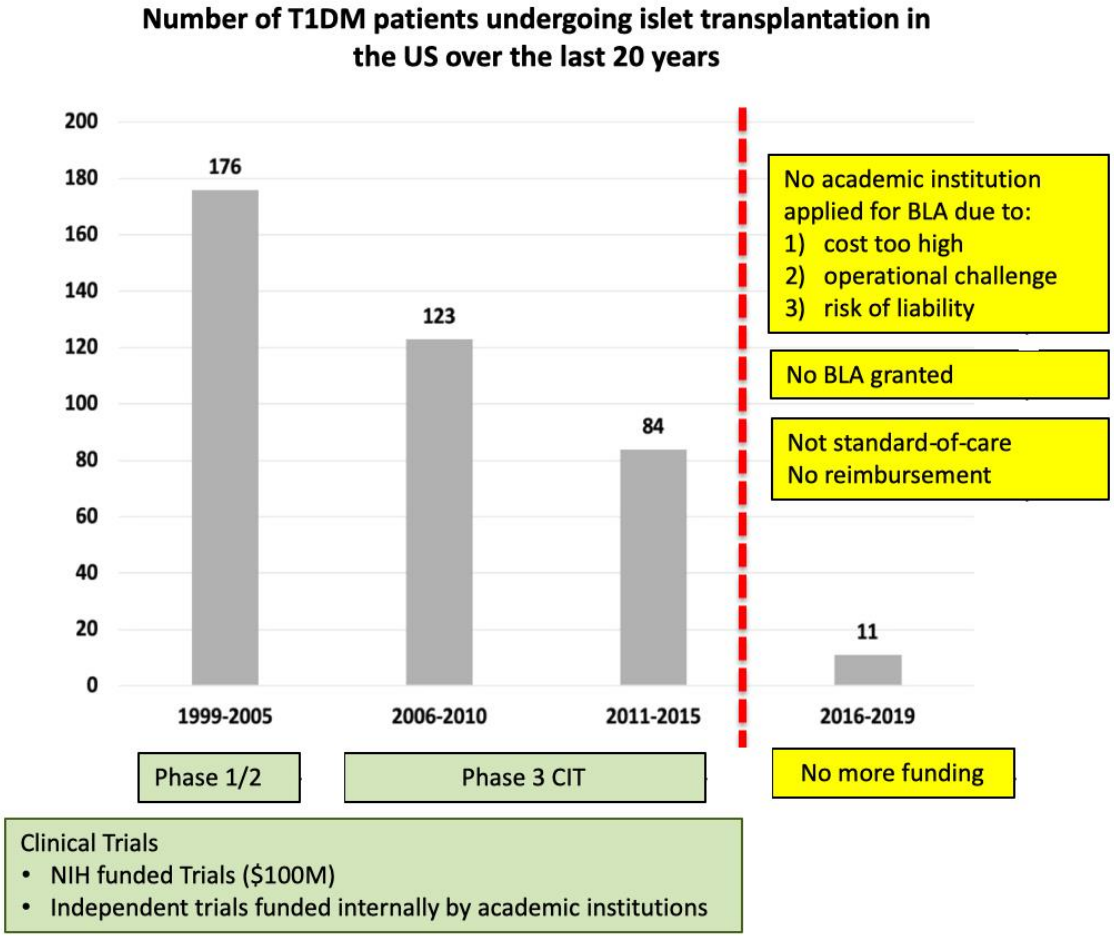
Figures and Tables

Figure 1. Catastrophic decline of allo-ITx procedures in the US

NIH- National Institute of Health; JDRF- Juvenile Diabetes Research Foundation;

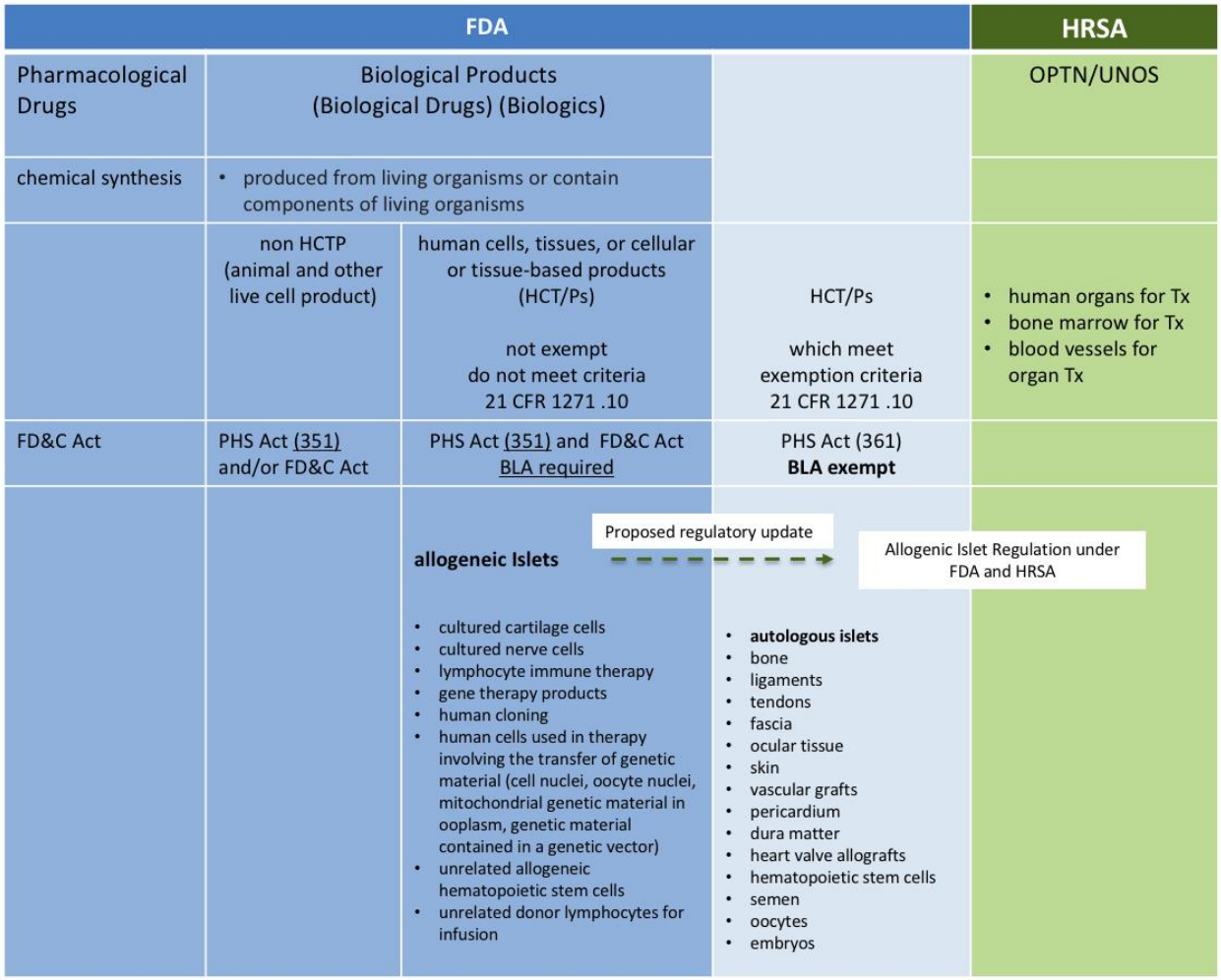
BLA- Biological License Application



Graph courtesy of Dr. Franca Barton, Clinical Islet Transplantation Registry, USA

Figure 2. Proposed regulatory updates in the US

(A) Details of the proposed regulatory framework



(B) Status of islet transplantation in the US and worldwide & the impact of the proposed regulatory updates

- Islet allografts subject to FDA investigational new drug (IND) regulations since 1993. (Table 1:16).
- 15 years of clinical research supported by over $100M of US taxpayer funding did not benefit US patients, although benefits are enjoyed by other patients worldwide; islet allograft processing was recognized by regulatory agencies worldwide as not being "substantially manipulated" based on US trial results and islets were exempt from BLA and regulated as a tissue/organ for transplantation instead of as drug or biologic.

- Islet transplantation is still not a standard-of-care procedure in the US, despite already being an established procedure in other countries.
- Islet allograft regulation as a drug by FDA resulted in a series of negative consequences. Situation will worsen after BLA is granted to a for-profit entity (negative consequences marked in yellow color).
- Proposed solution: regulatory update based on current scientific data from US clinical trials and CITR, which would result in islet exemption from BLA and the regulation of islets as organs with clinical oversight by OPTN/UNOS and islet processing according to specially tailored cGTP FDA regulations (dashed arrow).

EMA- European Medicine Agency (like FDA in US), ATMP – Advanced Therapy Medicinal Product, BLA- biological license application, CITR- Collaborative Islet Transplantation Registry, OPTN- Organ Procurement and Transplantation Network, UNOS- United Network for Organ Sharing, cGMP- current good manufacture practice, FDA- Food and Drug Administration

B)

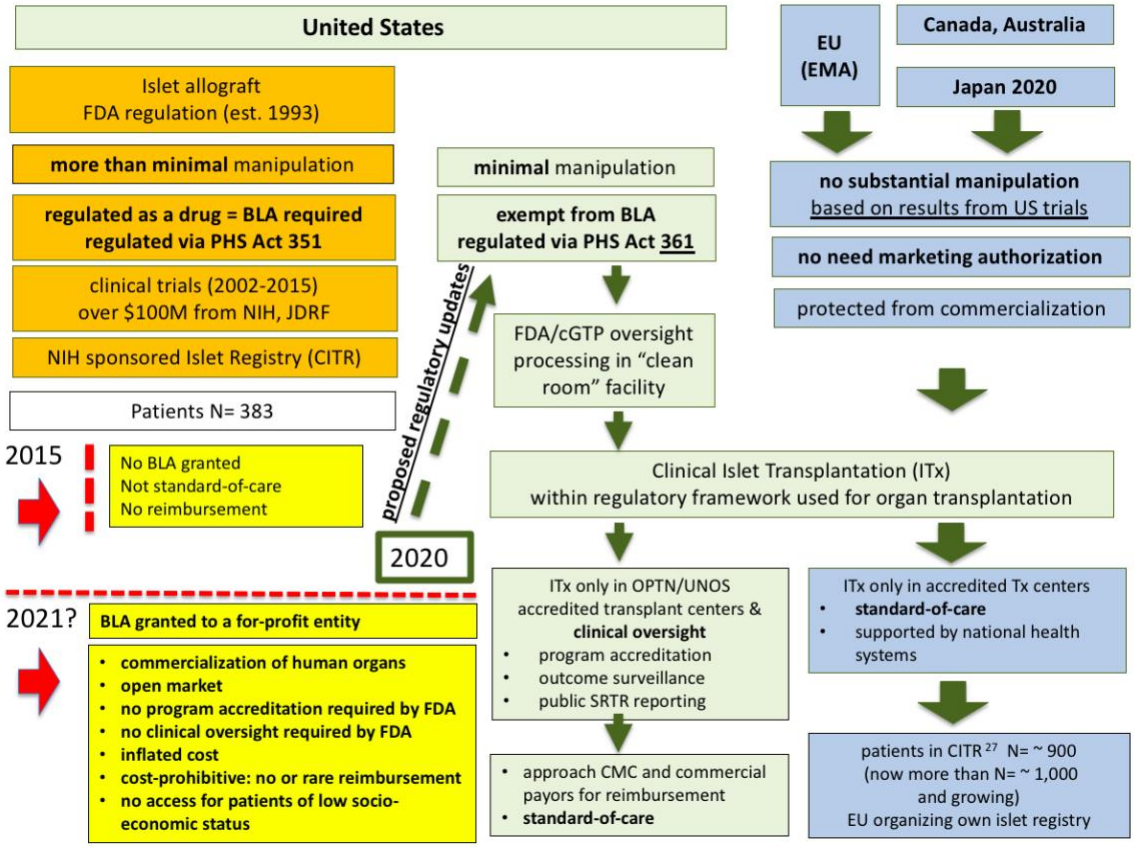


Table 1. Selected regulations and regulation related articles related to allo-ITx

	Regulations related to allo-ITx		
	Regulatory Agency	**Title of the regulation**	**Link to the source**
	Food and Drug Administration (FDA)		
1		Public Health Service Act Section 361 (United States Code, Title 42, Section 264) Human Tissue intended for Transplantation. Code of Federal Regulations. 21CFR Part 1270	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1270
2		Public Health Service Act Section 361 (United States Code, Title 42, Section 264) Human cells, tissues, and cellular and tissue-based products. Code of Federal Regulations 21CFR Part 1271	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=1271.10
3		Regulation of biological products. Public Health Service Act Section 351 (United States Code, Title 42, Section 262) Food, Drug and Cosmetic Act, Section 301 et seq. (United States Code, Title 21, Section 321 et seq.) Code of Federal Regulations, Title 21 Parts 600, 610	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=600 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=610 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=210 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211

		Code of Federal Regulations, Title 21, Parts 210, 211	
4		Orphan Drug Act Public Law 97-414 (enacted Jan. 4, 1983)	https://www.fda.gov/media/99546/download
5		FDA Database of Orphan Drug Designations and Approvals	https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm
6		Developing Products for Rare Diseases & Conditions	https://www.fda.gov/industry/developing-products-rare-diseases-conditions#About%20OOPD
7		Guidance for Industry and Food and Drug Administration Staff, Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue- Based Products: Minimal Manipulation and Homologous Use (2020)	https://www.fda.gov/media/109176/download
8		Guidance for Industry Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)	https://www.fda.gov/media/82724/download
9		Guidance for Industry Considerations for Allogeneic Pancreatic Islet Cell Products (2009)	https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Guidance-for-Industry--Considerations-for-Allogeneic-Pancreatic-Islet-Cell-Products-PDF.pdf
10		FDA's lisitng of BLA approvals by year	https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biological-approvals-year
11		Compliance Program Guidance Manual Chapter – 45 Biological Drug Products	https://www.fda.gov/media/73834/download#:~:text=Section%20501(a)(2,manufactured%20in%20compliance%20with%20CGMPs.&text=To%20help

			%20ensure%20the%20industry,each%20establishment%20at%20least%20biennially
12		Facts About the Current Good Manufacturing Practices (cGMPs)	https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps
13		FDA Type C Meeting Responses (Ref PTS#PS004003, CRMTS#11444), page 26. Type C Consortium Meeting to discuss and get FDA guidance about a possible facilitated path for islet transplantation by submitting one BLA to include five participating centers of the NIH CIT consortium	https://www.myast.org/sites/default/files/3-Islet%20Request-complete.pdf
14		Letter to PW from Sheryl Lard-Whiteford, Ph.D. Associate Director for Quality Assurance, CBER Product Jurisdiction Officer Center for Biologics Evaluation and Research US FDA	https://ce31f435-fd7c-460d-ab8a-6527449851e8.filesusr.com/ugd/e04a06_8a179bb8ca7a4ad9bc0792ffc582837e.pdf
15		Richard A. Merrill, Human Tissues and Reproductive Cloning: New Technologies Challenge FDA, Houston Journal of Health Law and Policy, Vol. 3, pp. 1-82	
16		Weber DJ, Mcfarland R, Irony I. Selected Food And Drug Administration Review Issues For Regulation Of Allogeneic Islets Of Langerhans As Somatic Cell Therapy. Transplantation. 2002,74:1816–1820.	
17		Weber DJ. FDA Regulation of Allogeneic Islets as a Biological Product Weber Cell Biochemistry and Biophysics, Supplement, 2004, 1085-9195/04/Supplement/40/19–22.	
18		Blood vessels recovered with organs and intended for use in organ transplantation. Final rule.	https://www.govinfo.gov/content/pkg/FR-2007-03-12/pdf/07-1131.pdf

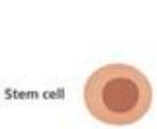
		Fed Regist. 2007;72(47):10922-10925.	
19	EMA – European Medicines Agency (EU) Committee for Advanced Therapies (CAT)	Reflexion paper on classification of advanced therapy products. 2015 May. EMA/CAT/600280/2010 rev.1	https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf
20		Good Manufacture Practice	https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice
21	HRSA/ OPTN (Health Resources & Services Administration/ Organ Procurement and Transplantation Network)	Federal law for organ transplantation, Charter	https://uscode.house.gov/view.xhtml?hl=false&edition=prelim&req=granuleid%3AUSC-2014-title42-section274&num=0
22		Final rule	https://optn.transplant.hrsa.gov/governance/about-the-optn/final-rule/
23		Polices	https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf
24		Bylaws	https://optn.transplant.hrsa.gov/governance/bylaws Appendix G outlines the membership and personnel requirements for the transplant programs

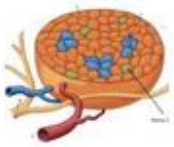
Supporting Information

Figure S1:

Islets and organs for transplant have similar characteristics in contrast to a single cell HCT/P (e.g. mesenchymal stem cells) and merit similar regulation to reassure safety and efficacy.

MSC- mesenchymal stem cell





	MSC	Islet	Kidney
Consists of many different type of cells, well organized to form one functional unit	No	Yes	Yes
Complex function with complex mechanism of modulation	No	Yes	Yes
Own blood vessels (arterioles and capillaries), innervated	No	Yes*	Yes
Needs to be vascularized to work	No	Yes	Yes
More than minimally manipulated prior to transplant	YES	NO	NO
For homologous use	No	YES	YES
Can be stored frozen, ready to use from a shelf	**YES**	**NO**	**NO**
Preserved alive up to 72 hours, but not frozen prior to application	Can be	**YES**	**YES**
Requires **subjective surgical assessment** during donor and organ selection and organ surgical procurement	NO	YES	YES
The same safety in unrelated and in related donor/recipient combinations after proper immunological matching	?	YES	YES
Ultimate quality assessment	in vitro, prior to clinical use	after the transplant, based on clinical outcome	after the transplant, based on clinical outcome
Required BLA for clinical use in Europe	**Yes**	**NO**	**NO**
Required BLA for safety and effectiveness in US	**Yes**	**yes, but should be exempt**	**NO**

* Fowler JL, Lee SS-Y, Wesner ZC, Olehnik SK, Kron SJ, Hara M. Three-Dimensional Analysis of the Human Pancreas. *Endocrinology*. 2018;159(3):1393-1400.

Table S1.

Selected publications related to allo-ITx:

Part A: List of selected publications presenting results of clinical trials in islet transplantations in the US.

Part B: List of publications describing the status of islet transplantation outside the US.

Part C: List of selected publications presenting results of clinical trials in islet transplantations outside the US.

Part D: List of publications presenting clinical studies with 50% 5-year insulin independence rate after allo-ITx.

Outstanding results in a number of the most experienced centers, as comparison to multicenter studies, permits us to forecast that improved outcome levels will be achieved more uniformly.

Part A	**Selected publications presenting results of clinical trials in islet transplantations in the US**		
	Study	**Autor, title**	**Reference**
1	Phase 1/2 Multicenter NIH/JDRF sponsored	Shapiro AMJ et al. International Trial of the Edmonton Protocol for Islet Transplantation.	N Engl J Med. 2006;355(13):1318-30.
2	Clinical Islet Transplantation Consortium (CITC) CIT-7 NIH sposored Phase 3	Hering BJ et al. Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia.	Diabetes Care. 2016;39(7):1230-40. • Primary endpoint-prevention from SHE and HbA1c<6.5 achieved in 87.5% subjects at 1 year and 72% at 2 year.
3	CITC CIT-07 NIH sposored Phase 3	Ricordi C et al. National Institutes of Health–Sponsored Clinical Islet Transplantation Consortium Phase 3 Trial: Manufacture of a Complex Cellular Product at Eight Processing Facilities.	Diabetes. 2016;65(11):3418-28.
4	CITC CIT-07	Consistency of Quantitative Scores of Hypoglycemia	Diabetes Technol Ther. 2015 Apr;17(4):235-42.

	NIH sposored Phase 3 (CIT-07)	Severity and Glycemic Lability and Comparison with Continuous Glucose Monitoring System Measures in Long-Standing Type 1 Diabetes	
5	CITC CIT-07 NIH sposored Phase 3	Foster ED et al. Improved Health-Related Quality of Life in a Phase 3 Islet Transplantation Trial in Type 1 Diabetes Complicated by Severe Hypoglycemia.	Diabetes Care. 2018;41(5):1001-8.
6	CIT-06 NIH sposored Phase 3	Markmann J et al. Phase 3 Trial of Human Islet-after-Kidney Transplantation in Type 1 Diabetes	AM J Transplant 2020, Jul 6. • Primary endpoint-prevention from SHE and HbA1c<6.5 achieved in 65% prevention at 1 year • A1c dropped from 8.1% to 6% at 1 year follow up and to 6.3% at year 2 and 3.
Part B	**Publication describing the status of islet transplantation outside the US**		
	Country	**Author, title**	**Reference**
1	Australia	O'Connell PJ et al. On behalf of the Australian Islet Transplant Consortium. Establishing a national program of islet transplantation in Australia.	CellR4. 2019;(7):e2797.
2	United Kingdom	Johson PRV. On behalf of the UK Islet Transplant Consortium (UKITC). Islet Transplantation in the UK.	CellR4. 2019;(7):e2788.
3	Switzerland	Berney T. Not reimbursing islet transplantation creates discrimination against patients with type 1 diabetes.	CellR4. 2019;(7):e2774.
4	Italy	Bertuzzi F. Islet	CellR4. 2019;(7):e2772.

		transplantation in Italy.	
5	Poland	Dębska-Ślizień A et al. Islet Transplantation – perspective from Poland.	CellR4. 2019;7:e2786.
6	Canada	Shapiro AMJ. Islet Transplantation – The Canadian Perspective.	CellR4. 2019;(7):e2799.
Part C	**Selected publications presenting results of clinical trials in islet transplantations outside the US**		
	Country	**Autor , title**	**Reference**
1	Australia	O'Connell PJ et al. Multicenter Australian Trial of Islet Transplantation: Improving Accessibility and Outcomes.	Am J Transplant. 2013;13(7):1850-58.
2	Canada	Senior PA et al. Islet Transplantation at the University of Alberta: Status Update and Review of Progress over the Last Decade.	Can J Diabetes. 2012;36(1):32-37.
3	France	Lablanche S et al. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial.	Lancet Diabetes Endocrinol. 2018;6(7):527-37.
4	France	Vantyghem MC et al. Ten-Year Outcome of Islet Alone or Islet After Kidney Transplantation in Type 1 Diabetes: A Prospective Parallel-Arm Cohort Study.	Diabetes Care. 2019;42(11):2042-49.
5	Netherlands	Nijhoff MF et al. Glycemic Stability Through Islet-After-Kidney Transplantation Using an Alemtuzumab-Based Induction Regimen	Am J Transplant. 2016;16(1):246-53.

		and Long-Term Triple-Maintenance Immunosuppression.	
6	Italy	Piemonti L et al. Alloantibody and Autoantibody Monitoring Predicts Islet Transplantation Outcome in Human Type 1 Diabetes.	Diabetes. 2013 May;62(5):1656-64.
7	United Kingdom	Brooks AMS et al. De Novo Donor-Specific HLA Antibodies Are Associated With Rapid Loss of Graft Function Following Islet Transplantation in Type 1 Diabetes.	Am J Transplant. 2015 Dec;15(12):3239-46.
8	Czech Republic	Voglová B et al. Benefits of Islet Transplantation as an Alternative to Pancreas Transplantation: Retrospective Study of More Than 10 Ten Years of Experience in a Single Center.	Rev Diabet Stud. 2017;14(1):10-21.
9	Norway	Schive SW et al. Cost and clinical outcome of islet transplantation in Norway 2010-2015.	Clin Transplant. 2017 Jan;31(1).
10	Poland	Golebiewska J et al. "Old school" islet purification based on unit gravity sedimentation as a rescue technique for successful intraportal islet transplantation– a case report	Cell Transplant 2020 in press
11	Sweden/ Norway/Finland	Sthle M et al. Evaluation of Perfluorohexyloctane/Polydimethylsiloxane for Pancreas Preservation for Clinical Islet Isolation and	Cell Transplant 2016 Dec 13;25(12):2269-76.

		Transplantation	
Part D	**Publications presenting clinical studies with 50% 5-year insulin independence rate after allo-ITx**		
	Study	**Author, title**	**Reference**
1	CITR cohort NIH sponsored	Bellin et al. Potent Induction Immunotherapy Promotes Long-Term Insulin Independence After Islet Transplantation in Type 1 Diabetes.	Am J Transplant. 2012;12(6):1576-83.
2	U Penn NIH sponsored (CIT-07)	Rickels MR et al. Improvement in β-Cell Secretory Capacity After Human Islet Transplantation According to the CIT07 Protocol.	Diabetes. 2013 Aug;62(8):2890–7.
3	UCSF/ U Minnesotta NIH/JDRF sposored	Posselt AM et al. Islet Transplantation in Type 1 Diabetics Using an Immunosuppressive Protocol Based on the Anti-LFA-1 Antibody Efalizumab.	Am J Transplant. 2010 Jul 23;10(8):1870–80.
4	U Minnesotta NIH supported	Hering BJ et al. Single-Donor, Marginal-Dose Islet Transplantation in Patients With Type 1 Diabetes	Diabetes. JAMA. 2005 Feb 16;293(7):830.
5	U Illinois (Chicago) NIH supported	Qi M et al. Five-year follow-up of patients with type 1 diabetes transplanted with allogeneic islets: the UIC experience.	Acta Diabetol. 2014;51(5):833-43.

Table S2.

Potential positive impacts of regulatory update for islet allografts as HCT/Ps

Positive effects of islet re-classification by the FDA	
1. Rapid implementation as a standard-of-care procedure in the US	• There is sufficient data from clinical trials and the Collaborative Islet Transplantation Registry demonstrating the safety and efficacy of allo-ITx. Reclassification would remove the final regulatory barrier precluding recognition of allo-ITx as a standard-of-care based on recommendations of experts and professional medical societies similar to other countries worldwide (Table S1:B,D,E).[7-10,22,24,25,28]
2. Rapid availability of the only minimally invasive therapy for patients with life-threatening T1DM-associated hypoglycemia	• Despite advancing technology and medical care, over 70,000 desperate patients with T1DM in the US remain in constant fear of sudden death from severe hypoglycemic episodes.[17-21] • The risk of sudden death is still a common threat despite the existence of the best medical treatment. A recent multicenter randomized trial noted that 1 out of 25 patients (4%) died due to severe hypoglycemic episode while receiving optimal insulin therapy at a university center.[22,23] • American patients should get the same access to islet transplantation as diabetics in Canada, Europe, Australia, and Asia.
3. Introduction of an insurance based reimbursement mechanism for the allo-ITx procedure	• Once regulations are updated, allo-ITx can be recommended as a standard-of-care by professional medical societies, and CMS and commercial payers will be approached for a reimbursement mechanism. (Of note, commercial payers have already indicated a strong interest in reimbursement for allo-ITx as it allows chronically sick patients to enjoy fast recovery and return to work because it is minimally invasive (personal communication)

	• The procedure will be performed only at OPTN accredited transplant centers, which meet all required standards for islet transplantation.
4. Further quality control of islet processing by the FDA	• Quality control of islet processing would continue to be regulated by the FDA, under cGMP and rules listed in 21 CFR Part 1271 Section 361 of the PHS Act (instead of extended regulations under Section 351 for biological products). Human islet processing laboratories (cGMP), as currently required, would be registered with the FDA, and would submit a list of each HCT/P manufactured. Labs would comply with other requirements contained in this regulation [66 FR 5466, Jan19, 2001, as amended in 69 FR, Nov 24, 2004].
5. Quality control of the procedure by OPTN/UNOS	• Surveillance of the quality of service and the related accreditation would be controlled based on expected outcomes in the same manner as for the transplantation of solid organs, which are currently regulated by the OPTN. Bylaws Appendix G outlines the membership and personnel requirements for programs. Similar to pancreas program, outcome measures including waitlist mortality rates, transplantation rates, and 1-year and 3-year patient survival, will be monitored by the OPTN and publicly reported by the Scientific Registry of Transplant Recipients (SRTR) on a bi-annual basis.
6. Centers for Medicare and Medicaid Services (CMS) oversight	• Once approved as a standard-of-care procedure, allo-ITx could be controlled by CMS regulations under the Code of Federal Regulation (CFR) as is already done for other clinical transplantation procedures. OPTN accreditation would be one of the requirement for the contract and reimbursement.
7. Positive impact on research and outcome improvement	• Allo-ITx research will become more affordable and robust. Insurance coverage of the standard-of-care part of the procedure will permit research funding to support more studies with more subjects. More transplant centers will be able to carry out the procedures so more studies can be conducted. Taken together, this will stimulate research and increase the likelihood for further

	advances, not only in allo-ITx but in beta-cell replacement therapy in general.
8. Positive impact on cost	• Cost of islet processing and transplantation will stay at the current level or may even decline as fixed costs will be amortized over a larger number of procedures. • Additional, unnecessary costs that are currently incurred from the preparation and implementation of BLA requirements ($3-4M per center, up front, with additional ongoing costs to comply with regulations) will be eliminated. • Not-for-profit academic centers would be able to provide safe and cost-effective treatments without having to recoup the costs related to a BLA application and subsequent operations.
9. Positive impact on the field of the regenerative medicine	• Advancement in islet (a micro organ) transplantation would trigger progress in regenerative medicine; in both, cellular therapies and in organ bioengineering.