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First update of the International Xenotransplantation Association consensus statement on conditions for undertaking clinical trials of porcine islet products in type 1 diabetes – Executive summary

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Abbreviations: cGMP, current Good Manufacturing Practices; CRISPR/Cas, clustered regularly interspaced short palindromic repeat/CRISPR-associated system; DPF, designated pathogen-free; EMEA, European Medicines Agency; FDA, Food and Drug Administration; GM, genetically modified; IE, islet equivalent; IXA, International Xenotransplantation Association; PERV, porcine endogenous retrovirus, NHP, non-human primate, TSE, transmissible spongiform encephalopathy; SAL, sterility assurance level; SACX, Secretary's Advisory Committee on Xenotransplantation; T1D, type 1 diabetes; TTS, The Transplantation Society, U.S., United States; WHA, World Health Assembly; WHO, World Health Organization

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Abstract

The International Xenotransplantation Association has updated its original 'Consensus Statement on Conditions for Undertaking Clinical Trials of Porcine Islet Products in Type 1 Diabetes', which was published in Xenotransplantation in 2009. This update is timely and important in light of scientific progress and changes in the regulatory framework pertinent to islet xenotransplantation.

Except for the chapter on 'Informed Consent', which has remained relevant in its 2009 version, all other chapters included in the initial consensus statement have been revised for inclusion in this update. These chapters will not provide complete revisions of the original chapters; rather they restate the key points made in 2009, emphasize new and under-appreciated topics not fully addressed in 2009, suggest relevant revisions, and communicate opinions that complement the consensus opinion. Chapter 1 provides an update on national regulatory frameworks addressing xenotransplantation. Chapter 2 a, previously Chapter 2, suggests several important revisions regarding the generation of suitable source pigs from the perspective of the prevention of xenozoonoses. The newly added Chapter 2a discusses conditions for the use of genetically modified source pigs in clinical islet xenotransplantation. Chapter 3 reviews porcine islet product manufacturing and release testing. Chapter 4 revisits the critically important topic of preclinical efficacy and safety data required to justify a clinical trial. The main achievements in the field of

transmission of all porcine microorganisms, the rationale for more proportionate recipient monitoring, and response plans are reviewed in Chapter 5. Patient selection criteria and circumstances where trials of islet xenotransplantation would be both medically and ethically justified are examined in Chapter 6 in the context of recent advances in alternative and available therapies for serious and potentially life-threatening complications of diabetes.

It is hoped that this first update of the International Xenotransplantation Association porcine islet transplant consensus statement will assist the islet xenotransplant scientific community, sponsors, regulators, and other stakeholders actively involved in the clinical translation of islet xenotransplantation.

Introduction

The International Xenotransplantation Association (IXA) published its original 'Consensus Statement on Conditions for Undertaking Clinical Trials of Porcine Islet Products in Type 1 Diabetes' in *Xenotransplantation* in 2009 [1-8]. To remain relevant, it was intended to update this initial consensus statement in light of changes in the regulatory framework, progress in research, and comments and perspectives communicated by stakeholders active in the field.

To provide a forum for an in-depth discussion aimed at providing the underpinning of the first update of the initial consensus statement, IXA convened a full-day conference in San Francisco, CA, on August 1, 2014. This conference was open to all members of IXA and was attended by an international multidisciplinary panel of scientists active in islet xenotransplantation and related fields. To those members not able to attend in person, an Adobe Connect line was provided to allow active participation in the conference. The recordings of the conference were made available online to IXA members after the meeting.

This first update of the IXA consensus statement, published in this issue of *Xenotransplantation*, is largely based on the discussion that took place at the above-referenced conference; also considered were the viewpoints communicated in scholarly review articles published on clinical translation of islet xenotransplantation since 2009 [9-11]. Included in this first update of the IXA consensus statement are this executive summary and seven chapters [12-18]. Except for the chapter on 'Informed Consent', which has remained relevant in its 2009 version [8], all other

chapters included in the initial consensus statement have been revised for inclusion in this update. These chapters are not to be viewed as complete revisions of the initial chapters; rather they restate the salient points made in 2009, highlight new and under-appreciated topics not fully addressed in 2009, suggest pertinent revisions, communicate opinions that complement the consensus opinion, and provide advice and information to those active and involved in clinical translation of islet xenotransplantation. Because many of the points made in the 2009 consensus statement remain valid, the reader is encouraged to study the chapters included in this issue in conjunction with the original chapters. The chapter on 'Genetically Modified Source Pigs' has been added as a new chapter in view of the increasing significance of such source pigs in islet xenotransplantation. The following paragraphs summarize the significant points made in the six updated chapters and in the one newly added chapter and restate the key points made on informed consent in xenotransplantation trials as presented in the 2009 Executive Summary.

Chapter 1: Update on national regulatory frameworks pertinent to clinical islet xenotransplantation [12]

Considerable progress has been made in developing and implementing regulations in several countries to empower national health authorities to effectively regulate xenotransplantation trials and thereby ban unregulated procedures.

1. The comprehensive guidelines for conducting xenotransplantation clinical trials established in the United States (US) since 1993 by the Food and Drug Administration (FDA) collaboratively with other agencies within the US Federal Government and with other national and international governing bodies addresses three fundamental goals: i) to provide a comprehensive approach for the regulation of xenotransplantation, ii) to address potential public health safety issues associated with xenotransplantation, and iii) to provide guidance to sponsors, manufacturers, and investigators regarding xenotransplantation product safety and clinical trial design monitoring [9]. In 2010, the FDA reviewed the existing regulatory framework within the US that would be applied to the regulation of clinical trials utilizing xenogeneic porcine pancreatic islets to treat T1D and outlined the general review principles with respect to the infectious disease status of the donor pigs, manufacturing and final product testing of islets, pre-clinical testing in animal models, and finally the design of the clinical trial [9].

2. Recognizing the global concerns over the conduct of uncontrolled and unregulated xenotransplantation practices, the World Health Organization (WHO) urged its member states in its World Health Assembly Resolution WHA57.18 to “allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place” [19]. Subsequently, the WHO convened WHO Global Consultations on Regulatory Requirements for Xenotransplantation Clinical Trials in Changsha, China in 2008 and in Geneva, Switzerland in 2011. WHA57.18 as well as the WHO Global Consultations emphasize the importance of international collaboration to prevent unregulated xenotransplantation and to coordinate xenotransplantation vigilance, surveillance and response to suspected infections. The recommendations for the roles and responsibilities for WHO, member states, and investigators of proposed xenotransplantation clinical trials, as outlined in the Changsha Communiqué [20], were reviewed in the initial IXA consensus statement [2]. The more recent ‘Geneva Consultation’ recommended to WHO i) to create a collaborative group of public/academic xeno-related infectious disease reference laboratories and appropriate health authorities’ resources to support assay development, validation, standardization, and sample throughput; ii) to encourage transparency in the development of national policies and procedures and in the conduct of any xenotransplantation trial to ensure harmonized practices and level of safety; and iii) to convene regular global consultations between regulators and xenotransplantation subject matter experts on xenotransplantation activities [21]. In addition, the ‘Geneva Consultation’ recommended to Member States, Investigators, Proposers, or Study Sponsors to i) seek global consistency in requirements for clinical trials by referring to best global standards and experts’ advice especially in areas such as source donor animal; recipients, family members and close contacts surveillance; risk/benefit analysis and trial infrastructure; ii) to combat unfounded assertions on human xenotransplantation; and iii) to assure access to independent (third-party) reference laboratories with identified expertise in xeno-specific infectious disease assays [21].
3. Several countries have embraced the suggestion of the WHO to harmonize xenotransplantation-related oversight and procedures on a more global scale [12]. Important changes of the regulatory framework pertinent to xenotransplantation have taken place or are in progress in several geographic areas that include the European Union, Korea, Japan and China. These changes encompass the most diverse facets of

the clinical application of xenotransplantation and comprise ethical aspects, source animals, and product specifications, study oversight, sample archiving, patient follow up, and extent to insurance coverage in some legislations.

Chapter 2a: Source Pigs - Preventing Xenozoonoses [13]

The original consensus statement set a reasonable bar at its time for the activities related to source pigs used in the preparation of clinical porcine islet products and still serves as an excellent platform from which to proceed given interim progress in the field [3]. A summary of salient revisions to the original consensus statement is as follows:

1. Donor animal pathogen screening strategy should be geographically appropriate, product specific, adaptive, and dynamic.
2. As new rapid diagnostic technologies are developed and validated, they may enable the direct screening of islet products themselves.
3. Encapsulated islet products present different risk profiles than non-encapsulated islets primarily due to the lack of recipient immunosuppression. Some encapsulation methods enable *in vitro* islet culture of sufficient duration to perform viral screening on islet products prior to transplantation.
4. While PERV-C negative donor animals could be considered preferable, PERV animal selection criteria should be primarily based on low PERV expression levels and lack of infectivity.
5. Biosecure DPF animal facilities built to agricultural standards could be considered as appropriate Source Animal Facilities if operated under SOPs and cGMPs.
6. The elimination of bovine products from the feed of donor animals throughout their lifetime should sufficiently mitigate the transmissible spongiform encephalopathy (TSE) risk.
7. The Sponsor's responsibility to archive donor samples should be for a limited duration and transferred to the appropriate regulatory government agency if additional duration is required.

Chapter 2b: Genetically Modified Source Pigs [14]

Chapter 2 of the first IXA porcine islet transplant consensus statement focused on the conditions required for source pigs to fulfill designated pathogen-free status [3]. However, the scope of the initial document did not extend to the use of genetically modified (GM) pigs as donors. Because of the increasing significance of GM pigs in islet xenotransplantation [22-24], it was imperative to include this dedicated new chapter in the updated consensus statement.

1. Genetic modification of the source pig offers the opportunity to improve the engraftment and survival of islet xenografts. The type of modification can be tailored to the transplant setting; for example, intraportal islet xenografts have been shown to benefit from the expression of anticoagulant and anti-inflammatory transgenes, whereas cytoprotective transgenes are probably more relevant for encapsulated islets.
2. The rapid development of pig genetic engineering, particularly with the introduction of genome editing techniques such as clustered regularly interspaced short palindromic repeat/CRISPR-associated system (CRISPR-Cas) [25-27], has accelerated the generation of new pig lines with multiple modifications. With preclinical testing in progress, it is an opportune time to consider any implications of genetic modification for the conditions for undertaking clinical trials.
3. Obviously, the stringent requirements to fulfill designated pathogen-free status that are applied to wild-type pigs will apply equally to GM source pigs.
4. In addition, it is important from a safety perspective that the genetic modifications are characterized at the molecular level (e.g., integration site, absence of off-target mutations), the phenotypic level (e.g. durability and stability of transgene expression), and the functional level (e.g. protection of islets in vitro or in vivo, absence of detrimental effects on insulin secretion).
5. The assessment of clinical trial protocols using GM pig islets will need to be done on a case-by-case basis, taking into account a range of factors including the particular genetic modification(s) and the site and method of delivery.

Chapter 3: Porcine islet product manufacturing and release testing criteria [15]

As in the first IXA porcine islet xenotransplant consensus statement [4], the pig islet product manufacturing quality and control requirements outlined here are based on the U.S. regulatory framework where these products fall within the definition of somatic cell therapy [28,29] under

the statutory authority of the U.S. FDA. In addition, porcine islet products require pre-market approval as a biologic product under the Public Health Services Act. Pig islet products also meet the definition of a drug under the Federal Food, Drug, and Cosmetic Act and are subject to applicable provisions of that law [30]. As with other somatic cell therapies and human islet products [31-33], the following criteria must be met for pig islet products before proceeding to clinical trials:

1. To facilitate control of manufacturing as well as reproducibility and consistency of product lots, the same general principles of current Good Manufacturing Practices (cGMP) that apply to human pharmaceuticals also apply to xenotransplantation products [9]. Data must be provided to demonstrate that islet products can be consistently prepared that would meet basic lot release requirements.
2. Sponsors intending to conduct a Phase 1 safety trial of islet xenotransplantation products can receive advice from regulatory agencies on whether the manufacturing of such products for a Phase 1 trial can be exempt from full cGMP compliance when the safety of the product can be demonstrated through the establishment of particular quality control and assurance procedures [34].
3. Procuring pancreata from a closed herd of pigs in an operating room located within the source animal facility and following SOPs for organ procurement, preservation and processing will assert considerable control over manufacturing. Similarly, if the final product is to be transported from the site of manufacturing to a distant clinical site, documentation is needed to show that under the proposed shipping conditions the islet products remain sterile, viable and potent.
4. To facilitate product safety, (i) materials used in the manufacturing process, including the pig pancreas, must be free of adventitious agents; (ii) islets must be manufactured using aseptic processing and (iii) the final product must undergo tests for sterility, mycoplasma (if cultured) and endotoxin. Safety specifications for pig islet product release include a negative Gram stain and an endotoxin content of <5.0 EU/kg recipient body weight. Product post-release assessments must include sterility cultures on the final product. Because results for sterility are available only retrospectively, a plan of action must be in place for patient notification and treatment in case the sterility culture results are positive for contamination.

5. Product characterization information should be acquired from a sample of the final product to be used for transplantation and must address important aspects of lot release testing [31] such as identity/purity (cell composition), quantity (islet equivalents [IE], cell number) and potency (insulin secretory capacity, oxygen consumption rate corrected for DNA or transplant bioassay in immunoincompetent diabetic mice) of the product; it also provides critical information to demonstrate manufacturing control and product consistency across multiple islet preparations (lots).
6. Providing islet products containing an islet mass sufficient to restore euglycemia in trial participants ($\geq 10\,000$ IE/kg) will require pooling of islets from multiple donor pancreata (≥ 2 to 4 from adult donors and ≥ 7 to 10 from neonatal donors). Demonstration of product consistency across products from individual pancreata would warrant release testing to be performed on a sample of the pooled product.
7. As product development and clinical trials advance, the increasingly more detailed specifications of potency assays on adult porcine islet products are expected to be predictive of post-transplant glycemic control. The immaturity of fetal and neonatal porcine islet tissue precludes the use of in vitro insulin secretion as a potency test as part of lot release testing unless demonstrated otherwise; another measure of potency appropriate to fetal and neonatal cells will need to be developed for product release testing and evaluation of aliquots of these products in mouse transplant bioassays should be performed to provide meaningful post-release information.
8. Several additional issues must be addressed when utilizing encapsulated xenogeneic islets for human transplantation [9]. All excipients used in the encapsulation process should either be pharmacopeial grade, or meet rigorous pre-determined analytical specifications. All critical process steps should be validated to establish the consistency and reproducibility of the islet encapsulation process. Information on the base biomaterial such as the source, molecular weight and molecular weight distribution/polydispersity, relative compositions of the subunits (for co-polymers such as alginate), purity, method of sterilization and the sterility assurance level (SAL) should be provided [9,35]. Furthermore, information on the properties of the formed capsule, such as size, thickness, homogeneity, porosity and permeability, stability and long-term durability, will need to be included [9]. Following

encapsulation a similar battery of tests to those listed in the previous section is necessary to confirm that this process has not adversely affected the viability, metabolic activity, or *in vitro* insulin secretory capacity of the islets [9,36].

Microscopic tests to determine capsule size, uniformity, and integrity are used to confirm that the encapsulated system has the physical properties required for free diffusion of lower MW components to and from the capsule whilst providing a sufficient barrier to immunological response. The assessment of the encapsulated islet product must also determine the number of islets within a capsule, the proportions of empty capsules and of unencapsulated cells, the bioreactivity and biocompatibility of the combined islet product and the device components. Specific defects may include the presence of an islet in the wall and a ruptured or distorted capsule. Assessment of the biological activity of the combined product is often a component of pre-clinical safety evaluations. It is recommended that studies should evaluate the duration and predictability of the device used in the combination product so that porcine islets contained in the device may be replaced at appropriate intervals to maintain life-supporting pharmacologic or metabolic activity.

Chapter 4: Pre-clinical efficacy and complication data required to justify a clinical trial [16]

The first IXA porcine islet xenotransplant consensus statement included IXA's opinion on what constituted "rigorous pre-clinical studies using the most relevant animal models" and were based on "non-human primate (NHP) testing" [5]. After careful consideration, it is believed there is a no need to greatly modify the conclusions and recommendations of the original consensus document.

1. Preclinical studies should be sufficiently rigorous to provide optimism that a clinical trial is likely to be safe and has a realistic chance of success, but need not be so demanding that success might only be achieved by very prolonged experimentation, as this would not be in the interests of patients whose quality of life might benefit immensely from a successful islet xenotransplant.
2. When "free" islets are being transplanted and immunosuppressive therapy will be necessary, it is not unreasonable to expect the investigators to demonstrate in the pig-to-NHP model that insulin-independence – or, at least, a greatly reduced insulin

requirement - can be achieved and maintained for several weeks or months in a small number of experiments. A successful result should be achieved with a clinically-tolerable immunosuppressive regimen. At the end of the period of follow-up, therefore, there should be evidence of functioning islets in the relative absence of complications from the immunosuppressive regimen, e.g., infection, malignancy.

3. While hesitant to provide definitive guidelines on the exact number of experiments in NHPs that is believed to be necessary to justify advancing to a clinical trial, the majority opinion is that successful reversal of diabetes in 4 of 6 (or 5 of 8) consecutive experiments would be sufficient to indicate potential success of a clinical trial. However, there was a significant minority opinion that the number of experiments required should not be generalized, but rather determined by the investigators themselves with regard to their research objectives, possibly after discussion with the relevant regulatory authorities. A majority of those consulted indicated that a minimum follow-up of 6 months is essential, with, ideally, follow-up for 12 months in one or more cases, and that any graft failure that occurs during these periods of time should not be a result of graft rejection.
4. If the patient who will receive the pig islet xenograft is already receiving immunosuppression for a kidney allograft, there is little additional risk associated with the xenotransplant. However, to suggest a potential benefit to the patient, it should be demonstrated that the immunosuppressive regimen used to prevent kidney allograft rejection is also likely to be effective in preventing islet xenograft rejection.
5. If “encapsulated” islets are to be transplanted without immunosuppression, then arguments for insisting on studies in NHPs are reduced. Nevertheless, the majority of those consulted believe that studies in NHPs are essential if the efficacy of islet xenotransplantation is to be proven. If any form of pharmacologic immunosuppressive therapy is found to be necessary, e.g., if the capsules do not provide complete immunoisolation, then studies in NHPs to exclude significant complications from this therapy are considered mandatory. If studies in NHPs are deemed necessary, the same (or similar) criteria regarding the number of experiments in NHPs and the length of follow-up should be followed as outlined below for the transplantation of “free” porcine islets. However, a shorter length of follow-up, e.g., 3 months rather than 6 months, was suggested by some of those consulted to be adequate when encapsulated islets are being tested, particularly when exchangeable devices would allow replenishment of islets.

6. Although it is believed that investigators should err on the side of caution, some flexibility in these guidelines is necessary if clinical trials of pig islet transplantation are not going to be unduly delayed.

Chapter 5: Recipient monitoring and response plan for preventing disease transmission [17]

Xenotransplantation of porcine cells, tissues and organs may be associated with the transmission of porcine microorganisms to the human recipient. The corresponding chapter of the initial IXA porcine islet consensus statement [6] focused on strategies to prevent transmission of porcine endogenous retroviruses (PERVs). The updated chapter summarizes the main achievements in the field since 2009 and addresses potential transmission of all porcine microorganisms including monitoring of the recipient and provides suggested approaches to the monitoring and prevention of disease transmission [17].

1. Prior analyses assumed that most microorganisms other than the endogenous retroviruses could be eliminated from donor animals under appropriate conditions which have been called “designated pathogen-free” (DPF) source animal production. PERVs, integrated as proviruses in the genome of all pigs cannot be eliminated in that manner and represent a unique risk.
2. Certain microorganisms are by nature difficult to eliminate even under DPF conditions; any such clinically relevant microorganisms should be included in pig screening programs.
3. With the use of porcine islets in clinical trials, special consideration has to be given to the presence of microorganisms in the porcine islet xenotransplantation products to be used and also to the potential use of encapsulation.
4. It is proposed that microorganisms absent in the donor animals by sensitive microbiological examination do not need to be monitored in the transplant recipient; this will reduce costs and screening requirements.
5. Valid detection assays for donor and manufacturing-derived microorganisms must be established. Special consideration is needed to preempt potential unknown pathogens which may pose a risk to the recipient.
6. Although the clinical application of porcine islet products will require a comprehensive plan for the testing and archiving of donor and recipient tissues, the absence to date of

reported in vivo transmission gives confidence that, with the appropriate safeguards in place, well-planned pilot clinical trials could be safely undertaken.

Chapter 6: Patient selection for pilot clinical trials of islet xenotransplantation [18]

A central element of the design of any clinical trial, especially of xenotransplantation and also of cellular and gene therapy early-phase trials, is the definition of the study population. The aim is to select a trial population with a favorable benefit-risk ratio, while protecting the public from undue risks and also achieving the study's scientific objectives [37-40].

The 2003 U.S. Food and Drug Administration (FDA) 'Guidance For Industry on Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans' and the 2007 Health Research Council of New Zealand Gene Technology Advisory Committee 'Guidelines for Preparation of Applications Involving Clinical Trials of Xenotransplantation in New Zealand' stipulate that, "because of the potentially serious public health risks of possible zoonotic infections, xenotransplantation should be limited to patients who i) have serious or life-threatening diseases for whom adequately safe and effective alternative therapies are not available except when very high assurance of safety can be demonstrated, ii) have potential for a clinically significant improvement with increased quality of life following the procedure, and iii) who are able to comply with public health measures as stated in the protocol, including long-term monitoring" [37,39]. The 2009 European Medicines Agency (EMA) Guideline on 'Xenogeneic Cell-Based Medicinal Products' similarly states that "the clinical development of xenogeneic cell-based products should involve initially patients with serious or life-threatening disease for whom adequately safe and effective alternative therapies are not available, or where there is a potential for a clinically relevant benefit" [38].

To identify, within this regulatory framework, suitable patient populations for early-phase clinical trials of xenogeneic islet cell products in diabetes, the following points should be considered:

1. Patients in whom T1D is complicated by impaired awareness of hypoglycemia and recurrent episodes of severe hypoglycemia are candidates for islet or pancreas transplantation if severe hypoglycemia persists after completion of a structured stepped care approach or a formalized medical optimization run-in period that provide access to hypoglycemia-specific education including behavioral therapies, insulin analogs, and diabetes technologies under the close supervision of a specialist hypoglycemia service.

2. Patients with T1D and end-stage renal failure who cannot meet clinically appropriate glycemic goals or continue to experience severe hypoglycemia after completion of a formalized medical optimization program under the guidance of an expert diabetes care team are candidates for islet or pancreas transplantation either simultaneously with or after a previous kidney transplant.
3. Similarly, patients with type 2 diabetes and problematic hypoglycemia or renal failure who meet these criteria are considered candidates for islet replacement.
4. Likewise, patients with pancreatectomy-induced diabetes in whom an islet autograft was not available or deemed inappropriate are candidates for islet or pancreas transplantation if extreme glycemic lability persists despite best medical therapy.
5. To justify participation of these transplant candidates in early-phase trials of porcine islet cell products, lack of timely access to islet or pancreas allotransplantation due to allosensitization, high islet dose requirements, or other factors, or alternatively, a more favorable benefit-risk determination associated with the xenoislet than the alloislet or allopancreas transplant must be demonstrated.
6. Additionally, in nonuremic xenoislet recipients, the risks associated with diabetes must be perceived to be more serious than the risks associated with the xenoislet product and the rejection prophylaxis, and in xenoislet recipients with renal failure, the xenoislet product and immunosuppression must not impact negatively on renal transplant outcomes.
7. The most appropriate patient group for islet xenotransplantation trials will be defined by the specific characteristics of each investigational xenoislet product and related technologies applied for preventing rejection. Selecting recipients who are more likely to experience prolonged benefits associated with the islet xenograft will help these patients comply with life-long monitoring and other public health measures.

Chapter 7 of the first IXA porcine islet xenotransplant consensus statement: Informed consent and xenotransplantation clinical trials [8]

This chapter has not been updated as all the points made in the 2009 consensus statement on informed consent in xenotransplantation clinical trials have remained relevant [8]. To include the discussion on this topic in the first update of the IXA porcine islet xenotransplant consensus

statement, the key points on informed consent as provided in the 2009 Executive Summary [1] are repeated below.

In international and national codes and guidelines involving human subject research and in the laws of many nations, the informed consent of research subjects is obligatory. The moral foundations of informed consent include and also extend beyond respect for individual persons as autonomous agents in Western nations. Axioms regarding the value of human life and duties to protect innocent and vulnerable persons from harm, duress and deceit underlie Western individualism and are broadly shared in many non-Western cultures. Accents on family and/or community consent in China and other nations are compatible with individual consent, as long as family and community consent supplement, rather than replace, individual consent.

Favorable harm-benefit determinations precede considerations of informed consent. When these harm-benefit assessments are favorable enough to warrant the onset of clinical trials, voluntary or freely given informed consent emerges as a pivotal moral precondition for these trials.

1. Xenotransplantation clinical trials involve a complex body of medical information, several procedures, numerous risks (associated with failure rates, immunosuppression, xenogeneic infections and so forth) as well as the subject's obligation to abide by extensive national and international precautionary guidelines. In obtaining informed consent, the following criteria must be ensured: Informed consent should be enacted preferably through an informed consent team as an organized, sequential, thoughtfully paced, jargon-free process of communication.
2. The consenting process must cover a large number of topics, including treatment choices, participation information, study procedures, information about risks associated with immunosuppression, discomforts and other matters, xenogeneic infections of recipients (and possibly close contacts and the community) and, due to infectious risks, the following 10 post-protocol subject responsibilities: (i) regular post-clinical research checkups, (ii) informing researchers of future changes of address/contact numbers, (iii) timely reporting of all unexplained illnesses, (iv) following present and updated behavioral guidelines with respect to exchanges of body fluids with intimate contacts, (v) no future donations of blood, sperm or other body fluids or tissues, (vi) autopsy at time of death, (vii) education of family members and intimate contacts about their need to take precautions associated with infectious disease risks – that includes offered educational

assistance from the research team, (viii) disclosure to future health care providers that subjects have received a xenotransplantation product, (ix) willingness to accept possible isolation and possible quarantine if necessary for public health and (x) arrangements for assistance in meeting future responsibilities should the subject lose decision-making capacity.

3. Due to the unknown infectious risks, subjects must be informed that, while they may withdraw from the medical interventions of the protocol, they must abide by their post-protocol responsibilities as stated here.

The Secretary's Advisory Committee on Xenotransplantation (SACX) of the U.S. Department of Health and Human Services has produced a draft document on informed consent containing a complete and understandable exemplary consent document for clinical research in xenotransplantation [28].

Conclusion

This 'First update of the IXA consensus statement on conditions for undertaking clinical trials of porcine islet products in type 1 diabetes' has been prepared by an international multidisciplinary panel of investigators with a long-standing involvement in islet xenotransplantation to assist the islet xenotransplant scientific community, sponsors, regulators, and other stakeholders in the clinical translation of islet xenotransplantation.

In light of the substantial progress made since the preparation of the initial consensus statement in 2009, all chapters except for Chapter 7 have been extensively updated. The advancements in developing and implementing regulations in several countries to empower national health authorities to effectively regulate xenotransplantation trials and ban unregulated xenotransplantation practices have been reviewed in Chapter 1. Several important revisions regarding the generation of DPF source pigs have been suggested in the Chapter 2a (previously Chapter 2). The progress on GM source pigs [22-24] and genome editing technologies [25-27] necessitated the addition of Chapter 2b. Early-phase clinical trials of transplantation of micro-encapsulated neonatal porcine islets have been completed under comprehensive regulation since 2009 [41], suggesting safety of transplantation of porcine islet xenotransplantation products when prepared from DPF source pigs in compliance with cGMP and transplanted into non-immunosuppressed recipients with T1D. Several updated chapters, in

particular Chapters 3, 4, and 6, have addressed the distinct circumstances of transplantation of encapsulated islet xenotransplantation products in the absence of immunosuppression. Chapter 4 provides a very thoughtful and balanced review of the critically important topic of preclinical efficacy and safety data required to justify a clinical trial and also includes minority opinions on the most relevant issues. The main achievements in the field of transmission of all porcine microorganisms, the rationale for more proportionate recipient monitoring, and response plans are reviewed in Chapter 5. Patient selection criteria and circumstances where trials of islet xenotransplantation would be both medically and ethically justified are examined in Chapter 6 in the context of recent advances in alternative and available therapies for serious and potentially life-threatening complications of diabetes.

Perhaps the most important remaining requirements to be met before clinical trials of porcine islet products in patients with diabetes can be initiated with more favorable and more definitive harm-benefit determinations are the development of a commercially viable porcine islet product and a clinically tolerable, effective, and available rejection prophylaxis [11,42]. The precise characteristics of the islet product deemed suitable for full clinical development and the precise immunosuppression, immunoisolation, or tolerance induction strategy selected for clinical development will determine the magnitude of the impact islet xenotransplantation can make in the care of diabetes for which several other competing technologies including beta cell replacement technologies are under development [43-46].

By involving essentially all investigators who are very active in the field and by inviting participation of all interested members of our professional society, the IXA has again taken proper, proactive and proportionate steps to outline a suitable framework for conducting clinical trials of porcine islet products in T1D without compromising unreasonably the safety of participants and the public. The IXA will continue to update this consensus statement as deemed appropriate in light of scientific advances, changes in the regulatory framework and comments submitted after publication. It is hoped that continued research, increasingly favorable safety and efficacy findings, and an improved understanding of the key factors affecting the harm-benefit determinations will build momentum to revisit with regulators the more challenging regulations and to engage funding agencies and industry to step up the commitment to developing porcine islet xenotransplantation products.

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Duality of Interest

B.J.H. has served as a consultant to Dompé s.p.a. and Janssen Research and Development L.L.C. and is a Director of Diabetes-Free, Inc.

E.C.

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G.R.R.

D.K.C.C.

J.D.

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