How Do We Move Type 1 Diabetes Immunotherapies Forward During the Current COVID-19 Pandemic?

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Research-based immunotherapy trials seeking to prevent or reverse a number of autoimmune diseases, including type 1 diabetes, have seen near universal suspension due to the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Diabetes and hyperglycemia are now appreciated as significant risk factors for COVID-19 morbidity and mortality; however, the vast majority of studies have reported on adults. Recent data in children and adolescents with type 1 diabetes suggest no increased risk of COVID-19. Even with immense appreciation for COVID-19 morbidity and mortality, we believe compelling arguments exist to carefully and thoughtfully resume certain type 1 diabetes phase 2–3 immunotherapy trials. In this Perspective, we consider the experience of trials that never halted or have resumed in the oncology and rheumatology fields, and advocate for staged type 1 diabetes immunotherapy trial resumption. With this, we present recommendations to achieve equipoise and mitigate risks for SARS-CoV-2 infection in the weeks surrounding infusion. Given the fact that the COVID-19 pandemic is expected to persist for some time, it is in the best interest of our patients that we find ways to safely move our field forward.

In response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, a variety of safety measures have been proposed to curb viral spread and thereby reduce coronavirus disease 2019 (COVID-19) morbidity and mortality (1). In January 2020, the U.S. Secretary of Health and Human Services declared COVID-19 a public health emergency, and in March, the U.S. Food and Drug Administration (FDA) issued nonbinding recommendations related to the conduct of clinical research with a subsequent update released in September 2020 (2). Resource allocation (e.g., personal protective equipment, hospital beds) and, of course, patient safety were central considerations for deciding whether to suspend enrollment or delay new trial initiation. Accordingly, March through May 2020 saw a dramatic decline in clinical trial enrollment worldwide across a variety of disease areas (3). Included in this action was a near universal decision to suspend research-based immunotherapy trials seeking to prevent or reverse a number of autoimmune diseases, including type 1 diabetes (4). Indeed, in the case of type 1 diabetes trials, which most commonly enroll children and young adults with uncomplicated prediabetes or recent-onset disease (5,6), the decision to halt experimental immunosuppressive interventions was a sensible one, particularly early in the pandemic when little was known regarding the impact of SARS-CoV-2 in patients with diabetes (7,8) and in the context of an altered endogenous immune response (9,10).

Increased Morbidity and Mortality in Individuals With COVID-19 and Diabetes

Initially, all forms of diabetes were considered a risk factor associated with increased COVID-19 fatality (11). In England, type 1 and type 2 diabetes were each individually associated with increased odds of COVID-19–related death (12), but poor blood glucose control and cardiovascular and renal complications coupled with reduced access to care during lockdowns imposed early in the pandemic may have influenced this observation (8). It is now well appreciated that risk of hospitalization and death is particularly elevated for COVID-19 patients with hyperglycemia regardless of underlying diabetes (13–15); moreover, obesity and older age, typically associated with type 2 diabetes,

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pose additional risk for poor outcomes in patients with COVID-19 (16). Indeed, the French CORONADO study demonstrated a dramatic difference in outcomes for hospitalized patients with COVID-19 and either type 1 or type 2 diabetes. Among those under 55 years of age, over 30% with type 2 diabetes died or required tracheal intubation in the first week of hospitalization compared with 12% of those having type 1 diabetes (17). Moreover, in a retrospective chart review, hospitalized adults with type 1 diabetes were reported to show similar clinical characteristics among those with and without COVID-19 (18). Importantly, though the vast majority of studies have reported on adults with diabetes and COVID-19, recent data in children and adolescents with type 1 diabetes suggest no increased risk of COVID-19 (19).

Simultaneously, concerns were raised regarding the potential for SARS-CoV-2 to exacerbate and/or induce diabetes (20,21). Indeed, COVID-19 has been associated with hyperglycemia and ketosis in people without diabetes as well as with worsened glycemic control in those with pre-existing diabetes (7,22). A relatively small epidemiological report from the U.K. appeared to support a causative link (23), while a larger German study did not (24). Histopathology studies of the human pancreas (25–27) are similarly conflicting regarding localization of ACE2, TMPRSS2, and TMPRSS4, which respectively serve as the SARS-CoV-2 receptor and cofactors for cellular entry (28), raising questions for how COVID-19 might cause glycemic dysregulation. The hyperglycemia-associated COVID-19 risk may not necessarily be associated with the presence or absence of endogenous insulin production, but regardless of the mechanisms at play, the apparent bidirectional relationship linking hyperglycemia and COVID-19 fatality underscores the need to preserve endogenous insulin production in people with or at-risk for type 1 diabetes.

Balancing Risk Versus Benefit in Type 1 Diabetes Immunotherapy Trials

In many ways, the concept of implementing caution in terms of therapeutic intervention is not a new one, as the type 1 diabetes research community has long struggled with issues regarding equipoise (29). Indeed, some of the most successful efforts noted to preserve β-cell function (e.g., cyclosporine, nonmyeloablative autologous bone marrow transplantation) (30,31) have effectively been abandoned due to both perceived and real issues of risk versus benefit, even in the absence of a COVID-19 environment. That said, in the current and evolving landscape of COVID-19, it is our hope that type 1 diabetes advocacy groups (e.g., JDRF, American Diabetes Association), funding agencies (e.g., National Institutes of Health [NIH], The Helmsley Charitable Trust), clinical research networks (e.g., NIH Type 1 Diabetes TrialNet [TrialNet], INNODIA, NIH Immune Tolerance Network), industry partners, and the type 1 diabetes patient community will engage in transparent and nuanced conversations regarding how and when to use immunotherapies in people with and at risk for the disease.

Timing of Intervention for Type 1 Diabetes

The incidence of type 1 diabetes is on the rise (32). In response, there have been increased efforts across the globe targeting the identification of at-risk people (33–36) toward the ultimate goal of preventing the eventual decline in functional β-cell mass. The disease pathogenesis begins years before clinical presentation with the development of islet autoantibodies, termed stage 1 type 1 diabetes (37). As β-cell destruction progresses, this is followed by the development of dysglycemia (impaired glucose tolerance, stage 2) before, finally, clinical symptoms of diabetes occur (stage 3 type 1 diabetes). Without a next step in terms of timeline for safely reinitiating immune therapy trials, many individuals will fall outside the time period when endogenous insulin production can be salvaged. Indeed, even before the COVID-19 era, potential subjects for type 1 diabetes trials faced short eligibility windows and limited study options when seeking research opportunities aimed at preserving remaining β-cell function.

Type 1 Diabetes Immunotherapy Trials Affected by COVID-19

Among the type 1 diabetes clinical trials utilizing immunosuppressive agents that were temporarily halted in the early spring of 2020, three are particularly noteworthy. A large multicenter phase 3 trial (NCT03875729) seeking to confirm the efficacy of teplizumab (anti-CD3) in new-onset (stage 3) type 1 diabetes was paused. Notably, this occurred despite results published in 2019 demonstrating that teplizumab had a unique ability to provide a significant delay (i.e., a median of 2 years) in the progression from stage 2 to stage 3 type 1 diabetes (38). With that, teplizumab sat on the verge of becoming the first immunotherapy to receive a label from the U.S. FDA and European Medicines Agency for preventing or delaying type 1 diabetes onset. As such, the cessation of recruiting for the current phase 3 teplizumab trial underscores the effects of COVID-19 on even the most promising agents. Similarly, NIH TrialNet, with guidance from its infectious disease committee, halted plans to move forward with prevention studies seeking to utilize rituximab (anti-CD20) plus abatacept (CTLA-4-Ig) (NCT03929601) and low-dose antithymocyte globulin (ATG) (NCT04291703). Notably, these agents, like teplizumab, have each individually demonstrated the ability to preserve β-cell function in new-onset type 1 diabetes (39–41).

At the same time, plans were implemented to move forward with a prevention study utilizing golimumab (anti-TNFα) given its positive effect in new-onset type 1 diabetes (42) and the suggestion that TNFα blockade may in fact reduce COVID-19 mortality risk (43). Notably, studies utilizing agents without perceived immunosuppressive effects (e.g., hydroxychloroquine [NCT03428945], proinsulin DNA

plasmid [NCT03895437], *Lactobacillus johnsonii* [NCT03961854 and NCT03961347]) continued enrollment despite limited previous clinical trial data to suggest a high likelihood of benefit. Here again, the allure of low-risk agents was potent, even more so during the COVID-19 era. Nevertheless, one must appreciate the fact that, to date, the track record of nonimmunosuppressive agents in the type 1 diabetes space has been disappointing (44,45). With perhaps the exception of oral insulin in a very small subset of patients (46) and the more recent suggestion that intralymphatic glutamic acid decarboxylase might afford benefit (47), low-risk, antigen-specific therapies and nonimmunosuppressing agents have been largely ineffective.

The New Normal for Type 1 Diabetes Immunotherapy

As our knowledge of SARS-CoV-2 has grown and we continue to observe that COVID-19 generally has similar effects in otherwise healthy young people with or without type 1 diabetes (15,19), the feasibility of safely conducting immunotherapy-based studies has come under consideration. Indeed, with the planet now fully enveloped in the realization of living through a prolonged pandemic, patient, advocacy, funding, and research communities alike began to question whether we could or, perhaps more importantly, should reopen type 1 diabetes studies utilizing immunotherapies. With this, late in the spring of 2020, certain research efforts slowly began to reemerge from a nearly complete shutdown, though the exponential rise in COVID-19–specific trials (3,594 trials related to COVID-19 or SARS-CoV-2 on ClinicalTrials.gov, access date 5 January 2021) dwarfed those in the ever-shrinking type 1 diabetes immunotherapy space (459 interventional trials in type 1 diabetes, determined on the same date).

Notably, in July 2020, two studies utilizing teplizumab (NCT03875729 and NCT04270942) were reopened at limited capacity with enrollment resuming only at centers where COVID-19 community rates remained under 5% positivity over the preceding 2-week period and with additional safety measures in place. Specifically, subjects were required to undergo COVID-19 testing prior to study drug administration, complete a 14-day post–study drug quarantine, and commit to ongoing social distancing and masking. Investigators were also urged to judiciously recruit subjects capable of personal automobile travel versus public transportation or airplane travel. Similarly, the European INNODIA network moved forward with their plans to open a phase 2, dose-ranging, efficacy study of ATG within 6 weeks of diagnosis of type 1 diabetes (MELD-ATG, NCT04509791), despite increasing community COVID-19 rates. The first subject in the MELD-ATG study was screened on 24 November 2020. The MELD-ATG effort similarly requires strict pre-infusion COVID-19 testing, post-infusion quarantining, and other mitigation strategies. Because cytokine release syndrome is both a feature of COVID-19 (48) and a known acute, but self-limited, adverse event associated ATG infusion (49), one can theorize that intervention with ATG may pose unique challenges in the era of COVID-19. However, a systematic review of clinical outcomes in SARS-CoV-2–positive kidney transplant recipients indicated that outcomes were not worse for recent transplant recipients who had received ATG (50). In addition, the cytokine release syndrome associated with ATG occurs only during the infusion itself and never recurs. As such, the likelihood of conflating ATG-related and COVID-19–related cytokine release in subjects known to be COVID-19–negative immediately prior to therapy is exceedingly low. The question therefore remains: does the risk of COVID-19 outweigh the potential benefits of participating in an immunotherapy study?

Type 1 Diabetes Can Learn From Efforts in Other Specialties

As a thought experiment, let us first consider the world of pediatric oncology, where immunotherapy studies within the children's oncology group were given explicit designation to continue despite COVID-19. Specifically, studies in children with standard-risk (NCT03914625) and high-risk (NCT03959085) leukemia, which combine chemotherapy with blinatumomab or inotuzimab, respectively, have continued unabated. As such, studies in children with both excellent and poor outcomes with standard care have continued even during the COVID-19 era. Cancer patients are known to have increased COVID-19 morbidity and mortality (51), though not all immunotherapies are equal in terms of the direction and degree to which they modify risk.

In continuation of our thought experiment, some might argue that a desire to continue oncology studies and a desire to continue type 1 diabetes studies are not exactly apples-to-apples comparisons. With that in mind, let us consider a potentially more analogous autoimmune diagnosis, inflammatory bowel disease (IBD). Notably, based on the worldwide database for IBD patients (SECURE-IBD), pediatric patients suffering from IBD have not had worse outcomes with COVID-19 even when utilizing combination immunosuppressive and immunomodulatory biological therapies (52). Within our own institution, there have been 15 cases of COVID-19 in adult IBD patients using dual therapy with biologics and immunomodulators. Notably, all 15 local patients have recovered, with only one requiring medical intervention. As such, nearly all IBD trials, including those using combinations of immunosuppressive and immunomodulatory biologics, have been reopened and are actively screening patients.

Similarly, two immunotherapy trials of Tadekinig alfa (recombinant human IL-18 binding protein) (NCT03512314 and NCT03113760) in the rheumatology space paused enrollment in April 2020 due to COVID-19 with activities fully resumed in July of that year. Meanwhile, a multicenter phase 3 trial of abatacept (CTLA-4-Ig) in oligoarticular juvenile idiopathic arthritis (NCT03841357) saw delayed initiation due to the COVID-19 pandemic but began nationwide subject enrollment in October 2020. These examples, in particular, underscore the willingness of trialists, patients, and families alike to move forward with immunotherapy studies for a variety of conditions in light of the risks related to COVID-19.

What Factors Should Drive Our Decisions?

While outcomes in neuro-oncology are objectively far worse than those in type 1 diabetes, we believe that people living with type 1 diabetes, IBD, and juvenile idiopathic arthritis share similarly challenging chronic diseases with significant risk of long-term complications and are worthy of every possible effort to continue seeking better outcomes through clinical trials. As such, we must continually reassess the status of our clinical trials and push back against the sometimes misplaced messaging used to suggest that type 1 diabetes is not a life-altering and even life-threatening diagnosis. Despite best efforts, more than 30% of new-onset type 1 diabetes patients present in diabetic ketoacidosis (53), and almost daily, one reads reports of patients dying due to lack of access to affordable insulin (54). In addition, despite access to markedly improving type 1 diabetes technologies, we must acknowledge that our field continues to fail when looking at the abysmally low percentage of patients who reach American Diabetes Association and International Society for Pediatric and Adolescent Diabetes hemoglobin A_{1c} targets associated with reduced diabetes complication risk (55). Of course, to more directly address these health disparities, particularly in the U.S., will require legislative action to implement universal and equitable access to affordable health care (56). However, we must again emphasize that this Perspective is not posed facetiously but indeed raises a question that deserves open discussion of the relative risks and benefits associated with exposure to SARS-CoV-2, clinical trial participation, immunotherapy, and life with type 1 diabetes.

While accepting that other rational and thoughtful people will come to different conclusions, our group advocates for the use of validated, effective COVID-19 mitigation strategies combined with staged reopening of sites to allow the resumption of previously paused type 1 diabetes clinical trials. Specifically, we believe priority should be given to reopening of trials with the highest likelihood of providing benefit, namely, those in which prior studies have shown the greatest capacity for β-cell preservation (Fig. 1). Sites should, of course, work with their respective institutional review boards (IRBs) to establish specific resumption protocols. Metrics whereby sites might consider enrolling subjects should likely include community positivity rates of less than 5%, with measures in place to again pause enrollment should positivity rates rise above this threshold. We acknowledge that this is an arbitrary cutoff, but we believe such a threshold represents a reasonable balance of risk versus benefit. In addition, we would require all subjects to have negative COVID-19 PCR testing reported within 72 h of study drug exposure. Furthermore, subjects must be willing to complete at least 2 weeks of post–immune therapy home quarantine (for agents like low-dose ATG) in order to minimize the risk of exposure during the period of most intense immunosuppression. Trial participants should also complete a COVID-19 risk assessment, subject to IRB approval, that codifies their understanding of the need to continue using appropriate social distancing and masking before and after their exposure to the study drug. Subjects must also be required to obtain influenza vaccination prior to therapy and should be up to date on all other vaccinations prior to study drug exposure (Table 1). Finally, with the recent European Medicines Agency authorization and FDA Emergency Use Authorization of two COVID-19 vaccines in individuals 16 years of age and older (57), investigative teams must consider timing of vaccination and exposure to immunomodulating study therapies in order to maximize COVID-19 protection.

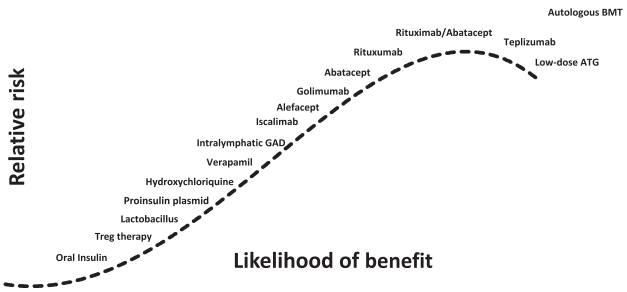

Figure 1— Conceptualized schematic representating relative risk vs. benefit for type 1 diabetes immunotherapies during COVID-19. Conceptual representation of the relative risk vs. likelihood of benefit associated with a number of previous studies and proposed type 1 diabetes interventions. In this nonquantitative schematic, the curve is not entirely linear, with some therapies near the very top of the likelihood of benefit scale, namely golimumab, being of slightly lower risk than other agents during the COVID-19 era. BMT, bone marrow transplantation; GAD, glutamic acid decarboxylase; Treg, regulatory T cell.

Timing of COVID-19 Vaccination

December 2020 simultaneously saw the widespread circulation of more transmissible SARS-CoV-2 variants (57) along with the worldwide commencement of mass immunization against COVID-19 (58). At the time of this writing, two vaccines have received authorization for use in people 16 years of age and older in both the U.S. and Europe (58–60), and trials are underway to evaluate their safety and efficacy in adolescents as young as 12 years of age (NCT04649151 and NCT04368728). In the U.S., access to either of the two approved COVID-19 vaccines varies appreciably by state or county (61) and, at present, is largely restricted to health care workers and residents of long-term care facilities (Phase 1a) (62). The Centers for Disease Control and Prevention recommends to next expand vaccination to "frontline essential workers" as well as individuals 75 years of age and older (Phase 1b) followed by people aged 65–74 years and individuals over 16 years of age with underlying medical conditions associated with increased COVID-19 morbidity and mortality (Phase 1c) (62). At this time, type 1 diabetes is not considered a condition that qualifies for Phase 1c, but JDRF is advocating for people with type 1 diabetes to be prioritized (63). However, as 2021 progresses, COVID-19 vaccines are expected to become more widely available to these groups and the remaining populace.

Table 1—Possible mitigation strategies for COVID-19 to permit reopening of immunomodulatory prevention and intervention studies in type 1 diabetes

COVID-19 rates*	14-day average positive rate <5% Negative slope of positivity trend line
Subject selection	Prestudy questionnaire regarding school, sports, work, and ability to quarantine demonstrates subject/family commitment to risk mitigation Preference for work from home or home school for at least 2 weeks post-infusion
Masking	Willing and able to wear mask at all times when outside of home for 2 weeks prior to and 2 weeks after study drug exposure
Travel	Travel by personal vehicle to and from study site No flights or use of public transportation (until travel/COVID-19 risk clarified) Remote study visits performed when able
COVID-19 testing	COVID-19 PCR negative result within 72 h of study drug exposure
COVID-19 vaccination**	For trial participants who are eligible for COVID-19 vaccination, complete vaccination course at least 2 weeks prior to study drug exposure
Quarantine***	Home quarantine other than essential activities with masking for 14 days following study drug

*Both the treatment site and subject's home community. **Timing of vaccination recommended here is based on the currently available mRNA-based COVID-19 vaccines produced by Pfizer-BioNTech and Moderna, both of which require two doses administered 3 or 4 weeks apart, respectively. At the time of this writing, both vaccines are approved for use in people 16 years of age and older, precluding vaccination of many eligible type 1 diabetes trial participants. As additional COVID-19 vaccines may be approved going forward, these should be independently evaluated for timing prior to study drug infusion. ***Specific metrics, timing, and duration of mitigation strategies may differ for different immune therapies based on their specific degree of immunosuppression and duration of biological activity. These suggestions are specific for the TrialNet low-dose ATG prevention study.

Both BNT162b2 produced by Pfizer-BioNTech and mRNA-1273 produced by ModernaTX, Inc. apply lipid nanoparticles to deliver mRNA encoding the SARS-CoV-2 spike protein and, thus, do not contain live virus. In both trials, serious adverse events were rare (0.6% for both vaccines) and occurred at rates similar to their respective placebo groups (58–60). Hence, we do not expect COVID-19 vaccination prior to experimental immunotherapy for type 1 diabetes to impart any additional or untoward risk. However, careful consideration must be given to the timing of vaccination, as certain immunomodulatory treatments may blunt vaccine efficacy. In adults aged 18–55 years who received BNT162b2, antigen-binding IgG and virus neutralizing antibody titers peaked in serum 1 week after the second vaccine dose (64). Similarly, mRNA-1273 induced a robust antigen-binding IgG response within 2 weeks of the first vaccine dose, with virus neutralizing antibodies peaking 1 week after the second dose (65). Additionally, SARS-CoV-2 spike protein–specific Th1 responses were detected 2 weeks after receiving the second mRNA-1273 dose (65). Hence, once COVID-19 vaccines become more widely available to the general public, we would recommend requiring trial participants to complete their full course of COVID-19 vaccination at least 2 weeks prior to receiving immunotherapy (Table 1). Trial participants should receive counsel on the risks of infection with SARS-CoV-2 as well as other common pathogens in the days to weeks following treatment, with guidance tailored to the specific study drug(s).

Strategies to Reduce COVID-19 Risk May Improve Safety of Immunomodulatory Therapies

The above-mentioned mitigation strategies, when appropriately applied, may actually make immunotherapy received during COVID-19 times safer than in the past. While at first glance this might appear a misstatement, consider the fact that pre–COVID-19, subjects would routinely fly long distances without masks, receive immunosuppressive therapies, fly home, go back to school, resume team sports, and return to "high-risk" job situations. Conversely, we would seek IRB approval to require patients participating in studies, at least at our center, to drive to us, making limited stops, to be tested for COVID-19 immediately before treatment, and to quarantine post-treatment during the peak period of immune suppression. As such, we posit that the risk for exposure (to any pathogen) is actually lower for subjects receiving immunotherapy now versus pre–COVID-19.

What Agents Should Be Considered?

With regard to specific agents, our group has been a strong advocate for the reopening of the previously approved TrialNet low-dose ATG prevention study (NCT04291703). By way of background, low-dose ATG has demonstrated the capacity to preserve β-cell function in both established and new-onset type 1 diabetes (41,66) and, in a cross-trial comparison, was shown to be more effective than any other "successful" immune intervention in the new-onset type 1 diabetes space, including teplizumab, at the 2-year study mark (5). As such, low-dose ATG has been extensively studied and has demonstrated the capacity to meaningfully affect long-term outcomes. Beyond this, we support the ongoing resumption of trials evaluating teplizumab, which significantly delayed type 1 diabetes onset in participants with stage 2 disease (38); of particular importance would be the phase 3 PROTECT study in individuals with recent-onset disease (NCT03875729). That said, other prevention studies using agents with efficacy in

the new-onset space should also be at the ready. The combination of abatacept/rituximab study (NCT03929601), while currently deemed high risk due to its proposed use of combined immunotherapeutics, should be fully prepared for implementation as soon as a SARS-CoV-2 vaccine is approved for use in people under 16 years of age. Arguably, the agents with the highest potential for benefit based on prior studies should be first in line to move toward reopening in a post-vaccine world.

Conclusions

When one appreciates that *1*) otherwise healthy young people with type 1 diabetes do not appear to have increased risk of COVID-19–associated morbidity and mortality (15,19), *2*) public health measures (e.g., masking, closures, restrictions on public gatherings, physical distancing) are effective in reducing exposure to SARS-CoV-2 (1), *3*) we have an ever-improving global capacity for and access to COVID-19 testing (67), and *4*) two vaccines have thus far been approved for emergency use in the U.S. and Europe, each reporting 94–95% efficacy in the prevention of COVID-19 (58–60), we believe compelling arguments exist to carefully and thoughtfully resume certain type 1 diabetes phase 2–3 immunotherapy trials when appropriate mitigation strategies can be applied to reduce risk and achieve equipoise (Table 1). We make this suggestion with immense appreciation for the morbidity and mortality associated with SARS-CoV-2 infection in the general populace (68–70), those with diabetes (7,8,12), and particularly among those being treated with immunosuppressive therapies (9,10). Nevertheless, given the fact that the COVID-19 pandemic is expected to persist for some time (71), we believe it is in the best interest of our patients that we find ways to safely move our field forward.

Simply put, given the lifelong challenges associated with a type 1 diabetes diagnosis and increased risk for diabetes-associated complications of COVID-19 (8,12,13), doing nothing is unacceptable. We advocate for staged trial resumption and have presented recommendations to mitigate risks for SARS-CoV-2 infection in the weeks surrounding infusion in children and adults enrolled in type 1 diabetes immunotherapy trials (Table 1). We must continue to keep equipoise in mind and appreciate that risk/benefit calculations will vary for different patients, families, interventions, and even doctors during this prolonged COVID-19 era. The dictums of primum non nocere (first, do no harm) and patient self-determination must both continue to be balanced. With that said, many centers have reopened for type 1 immunotherapy studies by carefully weighing the risks and benefits for each subject and enrolling only those who are fully prepared to follow all mitigation expectations. With the potential FDA approval of teplizumab on the horizon, immune therapy will likely become standard of care for delaying type 1 diabetes or prolonging the honeymoon phase in the near future. As such, conversations regarding equipoise will continue to be important for our field and, most importantly, for the patients we serve.

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