The Impact of COVID-19 on the State of Clinical and Laboratory Research Globally in Transplantation in May 2020

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INTRODCUTION

The impact of the COVID-19 pandemic is very wide and occupies almost every aspect of life across the world with the wave of direct health impacts cutting across each nation at different paces. The impact on the economies of all countries has been dramatic and has yet to become fully apparent. The effect of the pandemic on the health of transplant patients has been extensive with data published across a number of journals from both single centers and regional and national databases. It is becoming clear that transplant patients are more likely to catch SARS-CoV-2 and when infected have a much increased mortality risk. Impact on clinical services, through reduction in intensive care unit bed availability and decreased deceased organ donors, as well as diversion of clinical staff and other resources from transplantation, has led to dramatic decreases in clinical transplant activity. We have documented these impacts through the pages of Transplantation and through the COVID-19 Transplantation map established with the cooperation of The Transplantation Society.[1,2] What has not yet been documented to any degree so far is the impact on clinical and basic laboratory research in Transplantation. This round up of experiences from around the world shows substantial closure and diversion of effort from Transplantation research both in the clinic and in the laboratory with a future that is uncertain. Some countries and some centers have been more impacted than others. We hope by illuminating this feature of the pandemic we can assist in resuscitating research in our field as soon as compatible with the phases of the pandemic in each country.

LONDON, ENGLAND

With the recognition of the scale of the epidemic in the United Kingdom in early March, all research associated with our hospital unrelated to COVID-19 was closed with immediate effect. All research staff were redeployed to centrally funded COVID-19 studies. Plans to appoint new research staff were cancelled, and all research collaboration with international colleagues suspended. Clinically orientated basic research projects on liver transplantation have been deeply affected by these decisions.

Research projects put on hold include those on hepatic innate immunity and hepatocellular carcinoma in explanted livers, hepatocyte transplantation, and studies on hepatic innate and adaptive immune response. Clinical trials that involve antiviral therapies, posttransplant tolerance, and gut microbiota have also been put on hold as most patients are managed by virtual clinics and samples cannot be collected.

Research grants have been frozen with the majority of funding now directed to investigate COVID-19. Following the general community lockdown in late March, all clinical academics have been working fulltime on projects involving therapeutic trials for COVID-19. A project on posttransplant patients infected with COVID-19 is being formalized, however, sample collections will be problematic, since the majority of transplant patients are in self-isolation. Since March 2020, the number of new transplants performed has collapsed and the associated research projects have thus been put on hold for the lack of clinical samples. Research into the molecular and immunological mechanisms of ischemia/reperfusion damage and the impact of machine perfusion on marginal livers has been affected. We are currently not using marginal livers because of the potential for prolonged intensive care needs posttransplantation, the potential risk of infection, and the lack of junior personnel. Additionally laboratories have been closed down and all basic science research staff have been asked to stay at home for their safety. Now in May, some research staff are being released back from frontline duties, but it is not clear when transplant-related research can be resumed.

PERTH AND SYDNEY, AUSTRALIA

The COVID-19 pandemic has posed considerable challenges and uncertainty within the broad research environment in Australia, with enforced changes to the ability of

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researchers to conduct studies within the confine of the restrictions imposed by the research institute or hospitals. The National Health and Medical Research Council (NHMRC), Australia's peak body for research funding has acknowledged the difficulties in performing research during the pandemic and has made allowances for variations to the milestones for project completion. The current priorities for the NHMRC and the Australian Research Council are COVID-19-related research. Some of the current funding schemes for trials and cohort studies, and the Synergy grants initiative have been delayed and rescheduled, leaving financial and career uncertainties among our research staff.

At a local level, there have been important caveats when determining the continuation of study and trial activities, as opposed to the safety and willingness of participants to engage in these activities. The temporary discontinuation of acute kidney transplant services in Australia and the apprehension of excess immunosuppression in transplant recipients have led to the suspension of investigator and contract transplant study and trial activities. Although acute transplant service has recommenced in Australia in early May, there continues to be a general reluctance to reinitiate clinical research activities, in accordance with the advice and guidance of the NHMRC to prioritize the safety and well-being of research participants and staff. In addition, the decisions of hospitals and research institutions to impose restrictions on external personnel attending research centers, including study and trial participants have further added to the complexity of conducting research. Particularly affected are studies that assess the impact of modification of healthcare service and delivery on the health outcomes of vulnerable participants such as in children with chronic kidney disease or have received kidney transplants. The approach to recruitment and consent for participants in studies and trials has led to transformation from face- to-face recruitment to use of video conferencing and telephone, subjected to ethics committee approval. This has proved especially problematic for the recruitment of pediatric and adolescent participants of nonconsenting ages.

COVID-19 has had an equally severe effect on laboratory research, with trials of experimental therapies largely halted due to concerns related to the risk of COVID-19 and potential for increased severity of infections in affected individuals. Usual monitoring practices have become problematic, with closures of regional boundaries and shipping of samples to central laboratories has in some circumstances ceased. Furthermore, the impact of social distancing and closures of university campuses and institutes has limited laboratory work to critical experiments, which jeopardizes completion dates for students and limits data collection for future grant funding applications.

Although Australia has started to relax COVID-19 restriction, which may have a favorable impact on restarting and increasing current research activities, the engagement with international collaborators from "higher risk" countries with a greater number of COVID-19 cases remains very restricted. Each country is at a different phase of the pandemic response and research activities governed by their internal organizational structures are hetergeneous. Consequently, reliance on international collaborators to participate in jointly funded studies and trials remains unpredictable. The research landscape has changed with the effects likely to be felt for many years.

ROTTERDAM, THE NETHERLANDS

The laboratory research program at the Erasmus MC, Rotterdam, was mostly stopped on March 16, 2020. Since then, researchers have no longer been allowed to be physically present in the Erasmus MC. This was a far-reaching step which heavily impacted our laboratory research activities. Only for experiments with living material (cells and animals), laboratory personnel have been allowed to come to the research facilities to finalize experiments with all others working from home up to April 30. Our clinical research programs have been minimized, which impacted the transplant-related laboratory research. For example, hardly any patient blood and urine samples have been drawn and transferred to the laboratory for analysis. Also, no patients have been enrolled in (new) studies, and no new laboratory data have been generated. Consequently, our PhD students and postdocs swapped their priorities to writing manuscripts and grant proposals. Virtual laboratory meetings were organized to discuss progress and share information, which has worked quite well. As of early April, the number of people infected and hospitalized patients slowly declined, and scientists were allowed to restart their research under strict governmental (Dutch) guidelines. Of importance is that our employees (1) have to adhere to the principle of "social distancing," the 1.5-meter rule, and (2) continue to work from home as much as possible. We are currently working in shifts to limit the number of people in our facility and offices at any 1 time, while group meetings and supervision sessions are still performed online from home. As a result of the improved situation with fewer COVID-19 patients in our hospital, the transplant program also restarted, which together with the relaxed research guidelines improved "hands-on" work back to about 50%–60% of normal levels from May 15, 2020.

The clinical transplant program of the Erasmus MC was put on hold on March 13, 2020, and was restarted on May 7 when we performed the first living donor kidney transplant in 2 months. This patient was included in a prospective clinical trial. In the meantime, however, no patients have been included in de novo kidney transplant studies. In addition, no patients who are in the maintenance phase after transplantation have been included in any clinical study, apart from a validation study of a dried-blood spot analysis. We aim to fast track this dried-blood analysis method (which enables measurement of immunosuppressive drug concentrations and creatinine in a drop of blood) for clinical implementation, enabling minimization of patient visits to the outpatient clinic. Patients who were already participating in clinical studies have been followed as usual, with study visits combined as much as possible with routine outpatient checkups. The clinical research activities have been further impacted by the transfer of our transplant research nurses to the intensive care and hemodialysis units to take care of patients with COVID-19.

Much of the research on health behavior, self-management, and mental health of transplant patients incorporates face-to-face interviews or interventions. As such, upon the commencement of the lockdown in early March all these

research activities were put on hold. For example, outreaching interventions including home-visits are no longer possible. While it is certainly possible to translate a face-to-face intervention to a digital format, it is then essentially a different intervention. This has various methodological consequences. If we continue to deliver our interventions in an adapted format, we are concerned that the findings will not be comparable to the findings among participants in the pre-COVID-19 period. Can we cluster these groups together to maintain the power in the analysis? Might the pandemic influence the key outcomes and how might this affect our findings? We concluded that any continuation in an adapted form would be a significant protocol deviation and findings would therefore not be comparable. Finally, interventional research among transplant recipients that was due to commence in March or thereafter has been suspended until transplant programs are reestablished. One of the main challenges with such studies is the inclusion of sufficient patients to be able to demonstrate an effect. Anticipating difficulty recruiting participants in the outpatient clinic we have decided to postpone initiation of new studies until September 2020 in the hope that transplant programs will then be fully operational. PhD projects will therefore take longer to complete and require additional funding for the extension. Finally, while clinic-based research was put on hold we initiated a telephone interview study to assess the impact of the pandemic on the lives and mental health of patients who received a kidney transplant at our center (Dutch trial register NL8599).

NANTES, FRANCE

As a consequence of the national lockdown, which started on March 16, all research activities unrelated to COVID-19 have stopped at the Center for Research in Transplantation and Immunology, INSERM University of Nantes, as has been the case in most of the research laboratories in France. A major difficulty was that we were asked by our administrative authorities to shut down in just 2 or 3 days. This shutdown involved basic, preclinical, and clinical research programs and extended to a clinical trial in transplant patients due to start in 2022 in the context of an EU H2020 program RESHAPE. The consequences will be delay in clinical trials and clinical translation across a wide range of topics. The clinical activity was profoundly affected by the COVID-19 epidemic with the French kidney transplantation program halted. Given the urgency to better understand the pathophysiology of severe COVID-19, several immunologists, and virologists of our center have embarked on a new research project, written in 72 hours and funded by the National Research Agency. This has been a unique opportunity to develop collaboration with clinicians from Infectious Disease and intensive care units, which will allow for other projects in the future. Redeploying resources and expertise from our Center and from the associated Clinical Immunomonitoring platform to analyze immune responses in COVID-19 patients has been an interesting, necessary, and efficient process, though time consuming and with limited institutional support. Members of the center have also provided help to the hospital virology laboratory developing real-time polymerase chain reaction and serology assays for SARS-CoV-2 infection. For most of us, work during the lockdown has comprised writing research papers and reviews, online meetings, and planning new experiments once our confinement ends. New contracts for researchers due to start were mostly cancelled by the public institutions. Funding from the national agency of research and other sources have been pivoted to COVID-19 research, likely negatively impacting future funding in other areas.

The animal experimentation in our Center is performed in 2 distinct rodent facilities (in different buildings) and 1 large animal facility. All rodents in ongoing experiments were sacrificed with loss of many expensive experiments, and all colonies of animals from commercial vendors were euthanized. The only rodents kept, and to a minimal extend, are genetically modified rats and mice generated in-house. Primates were maintained for future experiments, but new projects have been delayed. A project on the generation of a genetically modified rat as a model of SARS-CoV-2 infection is due to start by the end of June.

The research laboratory has finally reopened on May 11, with very limited activity as we could only allow 10% of the staff to come into the laboratory for the first week and 20% for the second week. Priority has been given to projects involving third-year PhD students, last-year postdoctorates, nonpermanent young researchers, and experiments required to submit or revise publications and to support industrial partnerships.

REGENSBURG, GERMANY

Laboratory research activities at our institution in Germany have been limited since mid-March, but maintained at a basic level, as long as those activities did not utilize supplies or personnel that were potentially necessary for patient care during the early period of the COVID-19 outbreak. Widely used social distancing measures were utilized with reduced activities. In cases where human samples were collected as part of ongoing clinical research trials, all possible efforts were made within the guidelines to process and analyze those samples. While research personnel were reduced to an absolute minimum during the early period of the crisis, it has gradually become more apparent that our hospital capacity is not overloaded, so basic research activities are increasing and at this time are nearing a normal level. Research involving animal experiments remains highly restricted.

Research personnel during the most restrictive period of the slow down were allowed to enter the laboratories, but under controlled conditions. However, the majority had and used the option to work on research projects at home in the form of data analysis or article preparation. Return to the research laboratory has been most difficult for people with small children needing day care. If personnel were deemed essential for the care of patients, emergency day care was provided to least some degree by our institution. The restrictions on day care have very recently been loosened, allowing more possibilities for taking care of children so that parents can return to their research activities. Furthermore, in our region of Germany, classes for children up through high school are opening again for many, freeing up time for researchers to return to work under increasingly normal conditions.

The human ethics commission at our institution continued to operate with only slightly reduced capacity

throughout the COVID-19 crisis. While the highest priority was given to COVID-19-related studies, all other applications for human studies and trials were also processed. At present, there is essentially no reduced capacity with regard to handling human ethics applications.

BALTIMORE, USA

Institutional Review Board staff began working remotely at the beginning of March. All nonessential in-person laboratory activities, for both animal and clinical research, were shut down on March 18. Although telemedicine visits were supposed to be allowed for Research from that date, it was not actually allowed till May 11. Johns Hopkins University is postponing all external monitor on-site visits for clinical research protocols until at least May 31. All site initiation visits must take place remotely effective immediately and until at least May 31. On-site site initiation visits for COVID-19 trials and other life-saving trials may be allowed in exceptional circumstances where these may not be performed remotely. The Compliance Monitoring Program has cancelled all monitoring visits. At this time, no new compliance monitoring visits will be scheduled until after June 30, 2020. On-site monitoring visits will be rescheduled once restrictions on in-person meetings and recommendations for social distancing have been lifted. The Compliance Monitoring Program team members are available via e-mail and telephone for questions. All applicable institutional and regulatory requirements for human subjects' research continue to be followed, and proper documentation practices are maintained. The Fundamentals of Good Clinical Practice course has been offered via Zoom. The eIRB 1010 training sessions have been cancelled until further notice.

There is now a COVID-19 Biospecimen Committee, which evaluates requests from researchers for accessing serum or plasma from COVID-19 patients. The committee's default position will be for investigators to receive premade specimen collections for pilot studies with requests for custom made collections considered after pilot studies are completed.

There is a Tiered approach to Research and only Tier 1 studies are allowed with the Institutional Review Board totally focused on COVID protocols:

Tier 1—High Direct Benefit to Research Participants

Research in Tier 1 can continue if the principle investigator agrees the research can be conducted in a safe manner that protects subjects, research, and the community. There is a pause on enrolling new research participants unless there is a compelling reason and any in-person visits specifically for research purposes that require subjects to travel from out of state where the Governor of that state has issued a no travel order have ceased. All other in-person interactions may only continue for Tier 1 studies with a compelling justification to continue these interactions and the petition to continue is approved by the IRB. Studies at the Sidney Kimmel Cancer Center or JH-ACH must seek the approval to continue in-person activities from their respective review committees. COVID-19 studies may continue in-person interactions subject to IRB approval.

Tier 2—Moderate Direct Benefit to Research Participants

- Protocols in which research participants are receiving interventions or clinical care that is very interrelated to their research participation (eg, test results coming back that might have clinical implications for their care).
- Some protocols evaluating treatments for chronic conditions (eg, asthma, hypertension, depression, etc).
- Protocols involving assessment of the safety or efficacy of an intervention in which, if stopped, the potential societal benefit of the science would be significantly and adversely impacted, for example, where a research assessment (blood collection or imaging study) is only valuable if collected at a very specific time. This must be measured against the risk to participants, including the risk of exposure of COVID-19.

Research activities in Tier 2 must not enroll new participants in studies requiring in-person interaction nor continue to conduct in-person. The IRB will no longer consider requests to continue in-person activities for this Tier. Data collection that does not require in-person participant interaction (eg, telephone or online) may continue.

No new enrollment is permitted for Tier 2 studies.

Tier 3—Low Direct Benefit to Research Participants

- Cohort and natural history studies where delays in data collection have limited impact on scientific objectives.
- Protocols in which delays to starting or pausing of research does not substantively impact on research objectives of the research protocol.
- Protocols in which risks to research participants are higher (eg, potentially exposing elderly vulnerable individuals to COVID) and benefits of the study to the participants remain minimal.
- Research with healthy volunteers
- Any minimal risk studies that require research subjects to travel, that involve undergraduate students, or that are in a community setting and require direct interaction with researchers.

Research activities in Tier 3 must not enroll new participants in studies requiring face-to-face interaction nor continue to conduct face-to-face visits. Online visits or data collection that does not require participant interaction may continue.

LOUSIVILLE, UNITED STATES

Laboratory research and research based on experimental models were significantly impacted by university directed ramping down of nonessential research starting on March 11, 2020, followed by cessation of all nonessential basic science and clinical research activities on March 26, 2020. The university remained open; however, all researchers were strongly encouraged to perform data analysis and writing remotely and come into the university only if functions could not be performed at home. IT resources were made available to ensure secure access to research data and documents so that faculty and personnel could continue to work on data analysis, manuscripts,

and grant applications. Because of potential loss of animal facility personnel and the unknown duration of the COVID-19 pandemic policies, research animal stocks were depleted of all but critical strains and animals for essential research, which was defined as activity that if discontinued would cause significant and irreplaceable data loss or was required for maintenance of equipment, data, samples, animal populations. With specific approval from the Dean, faculty and staff could continue to conduct experiments for "essential" research. The current experimental transplantation experiments were not deemed essential, and there was some loss of commercially available strains of animals. However, these experiments will be able to restart as soon as the university gives permission. Time and effort cannot be charged to grant funds if experiments are not being conducted. In April and May, research staff and technicians who did not have sufficient work to perform at home were furloughed, which further increased the economic impact on laboratory research.

The transition to a remote research environment was fairly smooth. The university provided multiple platforms for online meetings and provided daily and weekly updates. All university-related domestic and international travel was banned, and campus events were cancelled or moved to online meetings. The remote research mandate for laboratory research has been extended to May 31 at least and a potential restart of all research and teaching is planned for the fall semester, assuming the COVID-19 infection rate continues to decline.

The brighter spots include the excellent communication between the university and research faculty and the community in general. Severe financial impacts have been distributed fairly and commercial animal vendors are offering a 25% discount to ease the financial burden of replacing the animals that were sacrificed in the shutdown. We have been able to use the time to reassess research direction, tidy-up neglected manuscripts and data, and prepare grants for shared equipment and improved research facilities.

Clinical transplantation research, with the exception of drug studies, or clinical trials that if stopped, might endanger study subjects, was put on hold by the pandemic. This was due primarily to cessation of all elective procedures at university affiliated hospitals, in preparation for large numbers of COVID-19 patients. Clinical research procedures deemed nonessential were halted, and those with federal funding were reported to regulatory agencies as on hold. These included studies related to function and physical therapy in hand transplant recipients and new mechanical circulatory support devices used to bridge critically ill patients to heart transplant. Experimental clinical trials such as the current study of allotransplantation of the hand have been put on hold, as was done by colleagues at other VCA centers in the United States. Follow-up of VCA study subjects is currently limited to telemedicine, and deviations have occurred with some study procedures, such as timing of blood draws to measure immunosuppression drug levels. Subjects were counseled that drug levels were critical to maintain their health and the health of their graft, but to use their judgement on the safety of exposure to COVID-19 at local health centers. Annual evaluations and other study interventions have been postponed until late summer/fall.

Where possible, solid organ transplantation data studies have continued as have procedures conducted in the course of standard clinical care of the patients. Of the 24 active clinical studies in transplantation, more than half could not continue. All living-related kidney transplants were postponed, resulting in a 10% reduction in volume of kidney recipients who could participate in research protocols. Deceased donor abdominal transplants continued as normal. All lung transplant candidates with a LAS of <50 and heart transplant candidates with a status of 4, 5, or 6 were put on hold, greatly reducing the number of available research candidates. Restrictions on travel imposed outside the university impacted the availability of on-site help for implant studies. There was also a transient lack of the ability to test donors for COVID-19 before transplant and potential donors were not accepted if COVID-19 status was unknown; however, this situation has now been resolved.

As with experimental studies, when clinical studies are placed on hold, personnel effort cannot be charged to the grant. We hope for, but cannot depend on, the extension of these funds to account for the time lost due to the pandemic. Time points in clinical studies will be altered. We do not predict significant impact on outcomes at this time. Our hospital and university administration performed admirably with daily, sometimes multiple daily communications via conference calls and e-mail 7 days a week. The University Institutional Review Board remained functional and continues to meet on a regular schedule online. Access to federal grant funding administration was and is also excellent, with no interruption in processing new awards or new grant applications. The university has remained open with online access to libraries and with hospital and university IT support to ensure that faculty had remote secure access to protected patient information.

CHICAGO, UNITED STATES

The University of Chicago research laboratories have been closed to non-COVID-19 research from the week of March 16, 2020. We had about 1 week to wind down experiments, and prepare the laboratory for a 4-week shutdown, which unfortunately was extended for another 6 weeks as a result of state mandate. We reduced our mouse colony by about 30%, keeping breeding cages and long-term posttransplant and control mice. We were allowed to designate 3 essential personnel to come into and check on the laboratory and to complete long-term experiments. However, we are not allowed to start new experiments or order supplies or mice, unless they are directly COVID-19 related. After over approximately 45 000 confirmed COVID-19 cases and 2000 deaths, the city of Chicago has seen the flattening in the numbers of new COVID-19 cases. Our institution has issued a plan for a phased research resumption, with on-campus research moving from the current 10% of pre-COVID-19 levels, to 25% and then 50% over the summer. We have developed a plan for safe return to work for our research team members exercising social distancing and safety measures, including working shifts, proper distancing at work space, utilizing personal protective equipment and sanitizers. Taken together, we anticipate that we will have no experiments involving the study of long-term posttransplant tolerant mice for at least

6 months and no short-term experimentation for at least 3 months. It has been especially challenging for the training of new students and postdocs in the laboratory and for postdocs hoping to complete their research and leave the laboratory this summer. Fortunately, no research personnel have been furloughed.

We have managed to maintain weekly meetings for the entire laboratory staff, meetings with smaller research groups, and interlaboratory meetings, using Zoom. These meetings have allowed postdocs, students, and technicians to work on finalizing figures and developing outlines of new manuscripts, and completing manuscripts for submission/resubmission. Some laboratory members have spent the time learning to analyze and present multiparameter flow cytometry data, while others learnt programming to analyze RNA-seq data. Finally, because we also conduct research in nanoparticulate vaccines, we have pivoted that research program to focus on SARS-CoV-2. We are leveraging rapidly developing institutional resources to support grant proposals on SARS-CoV-2 vaccines to the National Institutes of Health for funding.

Clinical non-COVID-19-related research has been reduced, maintaining only essential follow-up contacts, testing and procedures applying common rules for prevention of spreading the infection. Recruitment of new subjects has been on hold since March 16. Patients after participating in the interventional trial in kidney transplantation continue to come for outpatient intravenous infusion of the immunosuppressive study agent. Follow-up clinic visits have been limited and performed via telehealth. Our last patient with type 1 diabetes received islet transplantation at the beginning of March. She is currently insulin independent and without any complications. Patient went back home to Orlando, Florida, 1 week after the procedure and has been followed remotely. Remaining islet transplant and transplant study patients has been followed via telehealth utilizing blood testing at local laboratories. Planning ahead, we have already amended clinical study protocols addressing new risk related to COVID-19, implementing additional patient testing, infection prevention measures, remote telehealth visits, local laboratory, and home testing as well as electronic consents. All has been approved by our IRB. According to the university policy, such plan needs to be approved by the department chair. Since our clinical organ transplantation program has resumed full activity after adjustment to the current stage of pandemic in Chicago, we are expecting to resume clinical studies soon.