

**COMMENTARY**

# Insights and lessons learned from a prospective clinical pharmacology study in allogeneic hematopoietic stem cell transplant during the COVID-19 pandemic

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**To develop the first population pharmacokinetic (PopPK) model for oral tacrolimus in adult allogeneic hematopoietic cell transplant (allo-HCT) recipients, we conducted a prospective clinical pharmacology study among real-world patients (NCT04645667). This commentary describes the challenges associated with planning and executing the clinical pharmacology study during the global pandemic, and provides insights on how to effectively communicate, remain adaptable to institutional changes, improve consent rate, and to accommodate new clinical workflows and coronavirus disease 2019 (COVID-19) safety precautions without compromising the scientific integrity of the study.**

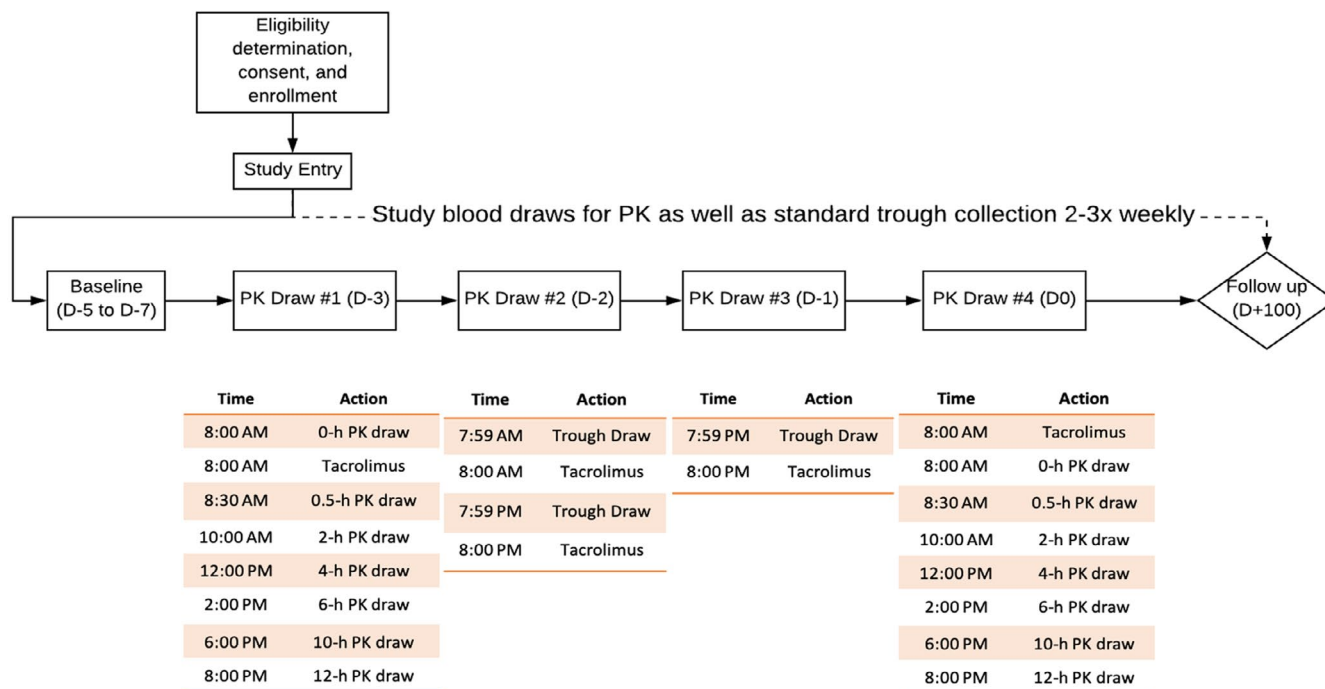
**INTRODUCTION**

Allo-HCT is a life-saving medical treatment for patients with both malignant and nonmalignant hematological diseases.<sup>1</sup> Tacrolimus is a cornerstone immunosuppressive therapy designed to prevent a potentially fatal clinical sequela following allo-HCT called acute graft-versus-host disease (aGVHD).<sup>2</sup> Tacrolimus has been approved by the US Food and Drug Administration (FDA) since 1994 for organ rejection prophylaxis in solid organ transplant settings, but never received an approved indication, with dosing guidance, for adult allo-HCT recipients.<sup>3</sup> As a narrow therapeutic index drug, tacrolimus has substantial pharmacokinetic (PK) interindividual variability, which can be attributed to differences in clinical and demographic characteristics (e.g., baseline organ function, concomitant medications, and germline genetics).<sup>4</sup> Interindividual PK variability necessitates the implementation of tacrolimus

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**FIGURE 1** PK sampling schematic. Study subjects are admitted to the UNC inpatient HCT unit 5–7 days prior to receiving their allo-HCT. The first day of the study occurs three days prior to the transplant date. The final day of the study occurs on the day of allo-HCT. Intense PK sampling is performed over the four days. Patient follow-up is conducted by monitoring the electronic medical record up to 100 days post-transplant to evaluate treatment-related toxicities and clinical outcomes. Abbreviations: allo-HCT, allogeneic hematopoietic cell transplant; D, day; h, hours; PK, pharmacokinetic; UNC, University of North Carolina

target concentration intervention to ensure that patients reach a target trough concentration range.<sup>5</sup> Currently, the tacrolimus starting dose is weight-based, and empirically adjusted for strong CYP3A4 inhibitors and inducers.

PopPK modeling can optimize dosing regimens based on patient-specific characteristics. Whereas over 80 PopPK models for tacrolimus have been previously described in the literature, we were the first to publish in allo-HCT. We repurposed a published tacrolimus PopPK model from kidney transplant recipients, and determined that their model described our sparse data well with a 10.3% mean absolute prediction error.<sup>6</sup> However, to develop a more robust tacrolimus PopPK model in adult allo-HCT recipients, where we account for HCT-specific covariates, we have initiated a prospective clinical pharmacology study with intense sampling of tacrolimus concentrations (ClinicalTrials.gov identifier NCT04645667; UNC IRB 19-3328). Previously, our group has also published associations between germline genetics, and both tacrolimus PKs and clinical outcomes. We concluded that *CYP3A5\*3* significantly associated with differences in tacrolimus trough concentrations at steady-state and time to target trough concentrations.<sup>7</sup> However, our prospective clinical study will ideally validate *CYP3A5* as a covariate in an allo-HCT PopPK model. Our intense sampling schema includes collecting 18 total blood samples,

starting 3 days prior to transplant and ending on the day of transplant (Figure 1). Clinical outcomes (e.g., aGVHD incidence and severity, and chimerism at 30, 60, and 90 days) and tacrolimus-induced toxicities (e.g., electrolyte abnormalities and acute kidney injury) are recorded prospectively for the first 100 days post-transplantation.<sup>8–10</sup>

The goal of this commentary is to provide our perspectives on the planning, initiation, and execution of a prospective clinical pharmacology study during the COVID-19 global pandemic. The major challenges we faced include study planning via remote access, patient enrollment, and adapting to clinical workflows with new COVID-19 safety precautions.

### INSIGHT 1: STUDY PLANNING REQUIRES ADAPTABILITY AND EFFICIENT COMMUNICATION TO ACCOMMODATE CHANGES IN INSTITUTIONAL RULES AND REGULATIONS DURING THE PANDEMIC

One major barrier to clinical research during the COVID-19 pandemic has been delays in timely communications between study team members. For instance,

feedback turnaround time for the initial draft of the study protocol from clinical advisors (i.e., attending physicians and clinical pharmacists) was greatly hampered by difficulties inherent to scheduling online meetings, and not having in-person discussions to hash out potential study opportunities and pitfalls. Our initial planning meeting was supposed to occur in-person in March 2020, and we struggled when we were forced to meet online during the initial stages of the pandemic, as all noninterventional clinical research operations were halted. Subsequently, when noninterventional clinical studies were allowed to restart at our institution in October 2020, communication between team members was still only virtual (e.g., online meetings and emails). However, by this stage, the physicians, advanced practice providers, clinical pharmacists, and study team personnel had become accustomed to online study planning activities because we had become increasingly efficiency familiar with online communication platforms. Ultimately, our online nursing in-service in February 2021 was a success, and we were able to discuss clinical study workflows details and implementation of new COVID-19 clinical research precautions.

Throughout the review and approval processes, coordination with regulatory committees was also conducted virtually, but occurred more infrequently because of reduced staffing in these departments. Staff reductions resulted in the delayed timeline for protocol, regulatory, and financial approvals, which negatively influenced the decision-making process by the study team. We were forced to acquiesce to having only email communications with our institutional Oncology Protocol Review Committee for scientific integrity, our Internal Review Board (IRB) for safety and ethics, and the reference laboratory that would quantify plasma tacrolimus concentrations.

Planning and initiating our study during the COVID-19 pandemic required the team to be adaptable to institutional operational rules and regulations changes, as they occurred almost on a daily basis. We originally decided to use flow cytometry to ascertain if nuclear factor of activated T-cell nuclear localization (NFAT) and interleukin-2 (IL-2) expression could be used as surrogate biomarkers of tacrolimus pharmacodynamics (PDs).<sup>11</sup> However, the pandemic limited our ability to conduct these planned PD biomarker analyses because of the limited number of core facility staff available to train users on the flow cytometers, and badge access limitations to the facility (only one-person per room). Ultimately, as we learned that during the pandemic, it was so important to strategically and efficiently communicate with institutional personnel from different disciplines so that we would receive and incorporate feedback in a timely manner. Despite barriers to study planning and initiation,

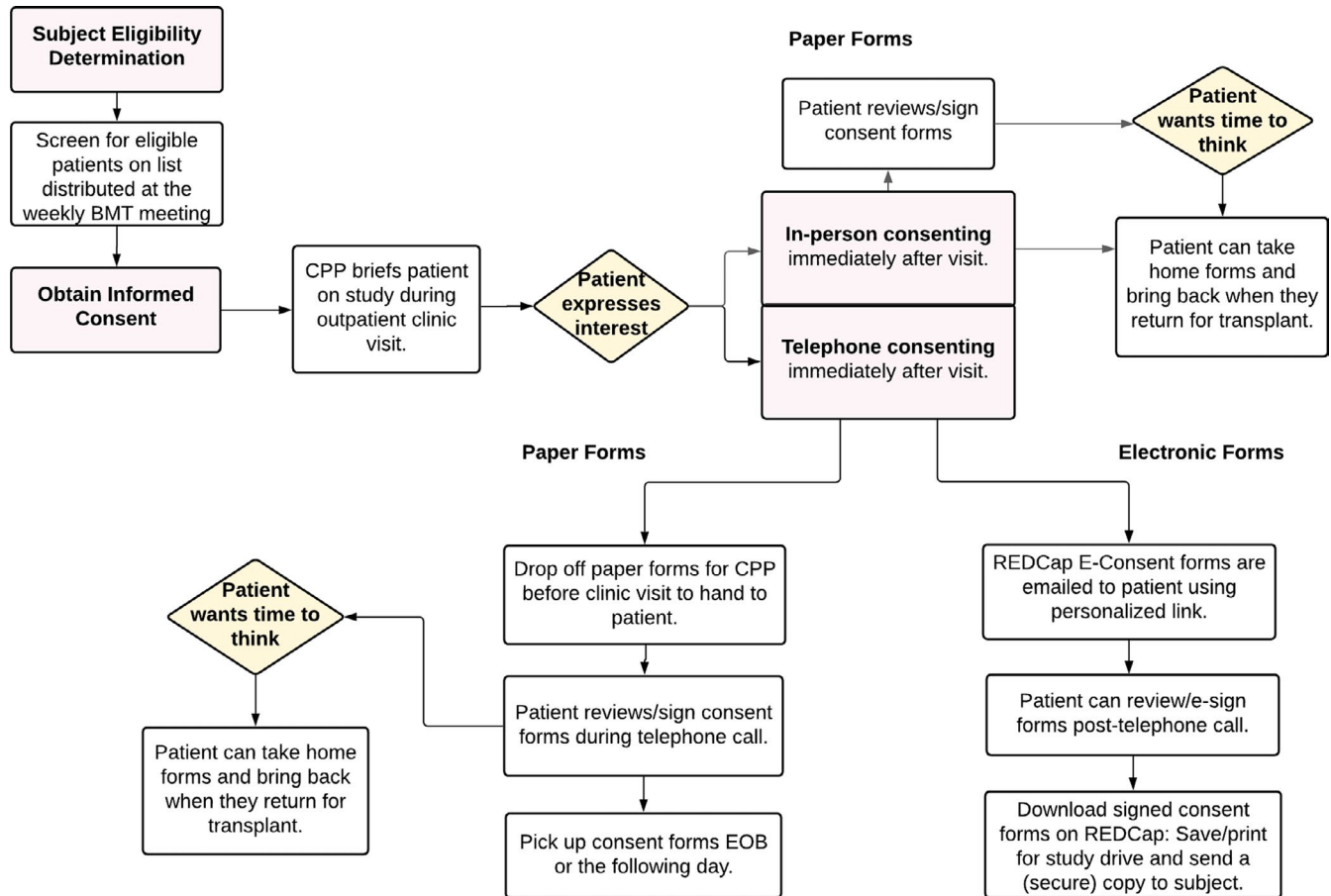
adaptability and efficient communication allowed us to accommodate institutional rules and regulations changes, and we successfully opened the study on February 1, 2021.

## **INSIGHT 2: INSURANCE APPROVAL WAS A CRUCIAL ELEMENT FOR SUCCESSFUL STUDY ENROLLMENT**

Study eligibility, due to third-party insurance reimbursement policies, was initially a major barrier to enrollment. The Centers for Medicare and Medicaid Services (CMS) “Coverage of Routine Services Associated with Clinical Trials” document ([tinyurl.com/yzpk6xuy](https://tinyurl.com/yzpk6xuy)) stated that the clinical trial must be a phase II, III, or IV patient research study for routine costs to be reimbursed. This meant there was initial ambiguity whether potential study participants would be eligible, based on reimbursement of transplant cost policies, if they had Medicare or Medicaid. Therefore, meticulous insurance verification was required prior to even approaching a participant to ensure we did not jeopardize reimbursement for the inpatient portion of their transplant. From February to May 2021, because we chose not to approach any Medicare and Medicaid patients, only 35% (6/17) allo-HCT recipients were eligible for consent. However, study team members continued to work with CMS and institutional liaisons to clarify whether allo-HCT recipients were eligible for enrollment. In May 2021, additional guidance from CMS and institutional liaisons clarified that Medicare and Medicaid patients are eligible for participation in prospective observational studies, which led to a 65% increase in eligible allo-HCT recipients (100%; 12/12). Clinician-scientists often lack the necessary background in health economics, institutional and health-system budgets, and the complexities of Medicare and Medicaid reimbursement. Despite a steep learning curve, having perseverance and diligence to work through the institutional policies for study budgets and insurance reimbursements is essential for a successful study launch and patient enrollment.

## **INSIGHT 3: IN-PERSON CONSENTING ASSOCIATES WITH HIGHER CONSENTING RATE, BUT MAY NOT BE FEASIBLE DURING THE PANDEMIC**

After confirming study eligibility, patients were approached, and informed consent was obtained either virtually, after their outpatient appointment with a clinical pharmacist, or upon admission to the inpatient HCT unit (Figure 2). Prior to performing in-person consenting,



**FIGURE 2** Patient enrollment process. This graph depicts patient screening and consenting workflow, which includes both telephone and in-person consent options. Abbreviations: BMT, bone marrow transplantation; CPP, clinical pharmacist practitioners; E-consent, electronic consenting platform; EOB, end of business day; REDCap, Research Electronic Data Capture

in accordance with the Centers for Disease Control and Prevention (CDC) recommendations for healthcare personnel (<https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control-recommendations.html>), non-provider study team members were among the first research personnel to receive a COVID-19 vaccination at the UNC Medical Center. We discovered in-person consenting to be more successful than virtual consenting, which we hypothesized was because the in-person consent process allows study team members to engender deeper connections to the study between themselves and subjects. From February to May 2021, when virtual consenting was the only option, 50% of patients (3/6) were successfully consented. However, in May 2021 when institutional rules allowed in-person consenting, the consent rate reached 92% (11/12). As of August 2021, we have successfully enrolled 14 out of a planned 50 subjects, the majority of which have been enrolled by in-person consenting. For future clinical studies, in-person consenting should be prioritized, if clinically feasible, but with proper telehealth training virtual consenting and enrollment can be successful.

#### **INSIGHT 4: COMPLIANCE WITH CLINICAL WORKFLOWS AND COVID-19 SAFETY PRECAUTIONS WITHOUT COMPROMISING SCIENTIFIC INTEGRITY IS CRUCIAL**

Conducting prospective clinical research studies prior to the pandemic was already challenging, but COVID-19 further complicated clinical workflows due to increased safety precautions. These included reduced inpatient HCT unit personnel (e.g., nursing), limitations on nonessential personnel entering the inpatient unit, and confirmed negative COVID-19 testing before entering the inpatient unit. Additionally, we were mindful to not adversely affect nursing workflows. At our institution, adult allo-HCT recipients receive the first dose of tacrolimus at approximately the same time as one of their conditioning chemotherapy regimen infusions. To respect nursing workflows, a 20-min window around the scheduled sampling time point was instituted for each tacrolimus PK draw. We also designed a PK sampling workflow sheet for the nursing



staff to ensure accuracy of the draws, while not upsetting other aspects of their work. Because each nurse is assigned to a different patient daily, the workflow sheet also served as a record of the PK sampling performed throughout the intense sampling portion of the study. When clinical resources are limited, extra assurance measures were needed to ensure that adapting to new clinical workflows did not compromise scientific integrity of the study.

## SUMMARY AND FINAL REFLECTIONS

The overall goal of this ongoing prospective clinical pharmacology study is to develop the first tacrolimus PopPK model among adult allo-HCT recipients, but our team was forced to contend with substantial barriers caused by one of the worst recorded global pandemics in modern history. Despite COVID-19, we gained valuable insights and learned new ways to communicate with patients, clinicians, and other institutional stakeholders. We learned to adapt the study focus to cope with new institutional rules and regulations, and we were educated on health economics concepts that helped us navigate third-party insurance approval process roadblocks. We instituted safe and effective in-person consenting procedures, and implemented creative measures to accommodate the new clinical workflows designed to address COVID-19 safety precautions, while simultaneously ensuring that the scientific integrity of the study was not compromised. Overall, we believe these insights could provide a successful roadmap for investigators seeking to launch a prospective clinical pharmacology study as the COVID-19 pandemic persists.

## CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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