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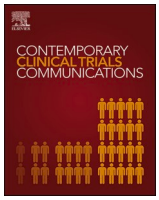

A point-of-care pharmacokinetic/pharmacodynamic trial in critically ill children: Study design and feasibility

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ABSTRACT

Background: High-quality, efficient, pharmacokinetic (PK), pharmacodynamic (PD), and safety studies in children are needed. Point-of-care trials in adults have facilitated clinical trial participation for patients and providers, minimized the disruption of clinical workflow, and capitalized on routine data collection. The feasibility and value of point-of-care trials to study PK/PD in children are unknown, but appear promising. The Opportunistic PK/PD Trial in Critically Ill Children with Heart Disease (OPTIC) is a programmatic point-of-care approach to PK/PD trials in critically ill children that seeks to overcome barriers of traditional pediatric PK/PD studies to generate safety, efficacy, PK, and PD data across multiple medications, ages, and disease processes.

Methods: This prospective, open-label, non-randomized point-of-care trial will characterize the PK/PD and safety of multiple drugs given per routine care to critically ill children with heart disease using opportunistic and scavenged biospecimen samples and data collected from the electronic health record. OPTIC has one informed consent form with drug-specific appendices, streamlining study structure and institutional review board approval. OPTIC capitalizes on routine data collection through multiple data sources that automatically capture demographics, medications, laboratory values, vital signs, flowsheets, and other clinical data. This innovative automatic data collection minimizes the burden of data collection and facilitates trial conduct. Data will be validated across sources to ensure accuracy of dataset variables.

Discussion: OPTIC's point-of-care trial design and automated data acquisition via the electronic health record may provide a mechanism for conducting minimal risk, minimal burden, high efficiency trials and support drug development in historically understudied patient populations.

Trial registration: clinicaltrials.gov number: NCT05055830. Registered on September 24, 2021.

1. Background

Children are therapeutic orphans, and most drugs remain understudied in pediatric populations [1]. The United States (U.S.) Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other regulatory agencies worldwide have established incentives and mandates to stimulate pediatric drug development [2,3]. Their regulations often permit some level of extrapolation of efficacy data from adult trials, but generally, all require a population-specific assessment of a drug's pharmacokinetic (PK) profile, and in some instances, a drug's pharmacodynamic (PD) profile. Therefore, despite the significant progress in the number of pediatric trials and the amount of pediatric use information, there remains a need to conduct high-quality, efficient PK/PD and safety studies in children. Unfortunately, there are several challenges inherent to PK/PD trials in children, as shown in Table 1 [1,4–6]. The challenges are accentuated in special populations, such as critically ill children and those with rare diseases [7]. As a result, these populations are often excluded from PK/PD clinical trials even though they are at highest risk of inadequate drug exposure (subtherapeutic or toxic) owing to the extensive effects of age- and disease-related factors on drug PK and PD [1,8,9]. Consequently, there is a need to identify practical approaches to conduct high-quality PK/PD trials in critically ill children.

Point-of-care trial designs that integrate clinical trials into routine medical care are gaining popularity in adult research [10,11]. These trials offer feasibility advantages including facilitating clinical trial participation for patients and providers, minimizing the disruption of clinical workflow, and capitalizing on routine data collection.

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Table 1
Challenges of pharmacokinetic/pharmacodynamic trials in children.

Patient Factors	Trial Design and Conduct	Infrastructure
Rare disease processes (small patient populations)	Rigid sample timing	Lack of pediatric pharmacology expertise to design, conduct, and analyze data
Low rates of parental consent	Lack of application of opportunistic methodologies to study drugs in children	Cost of maintaining an infrastructure to support pediatric clinical trials
Limited blood volume	Lack of validated clinical endpoints	

Point-of-care trials are not routinely used in pediatric therapeutics research, but offer a unique, minimal-risk, minimal-burden opportunity to study the PK/PD of drugs given per routine care and overcome many of the challenges shown in Table 1. Point-of-care trials leverage data extensively and prospectively documented in the electronic health record (EHR) per routine care, such as laboratory collection time, date, and value, medication time, route, and dose, vital signs, and diagnoses, and can be readily gathered from the EHR without the time and cost burden of additional trial-specific data collection [12–14]. Although point-of-care trials are inherently dependent on sparse and/or opportunistic sampling models, population PK/PD modelling and simulation can be used to overcome this [2,7,13,15,16] since PK/PD data can be generated to validate and standardize efficacy and safety targets.

Critically ill children with heart disease are an ideal population in which to evaluate the feasibility of the point-of-care trial design due to the comprehensive nature of routine intensive care unit (ICU) care and the need for PK/PD studies in this population. Critically ill children receive a median of 9 drugs, undergo a median of 38 lab draws, and have frequent, if not continuous, vital sign monitoring during their ICU stay [17,18]. Small, single-drug, PK studies have successfully integrated opportunistic sampling with EHR data, but each single-drug study must gain funding, develop a protocol and statistical analysis plan, obtain approval by an institutional review board (IRB), and consent children separately [6,13,15]. Here we describe the design of the novel point-of-care Opportunistic PK/PD Trial In Critically Ill Children with Heart Disease (OPTIC, NCT05055830). OPTIC represents a programmatic point-of-care approach to PK/PD trials in children, consisting of a centralized study protocol with iterative additions of drugs of interest. OPTIC seeks to overcome barriers of traditional pediatric PK/PD studies to generate safety, efficacy, PK, and PD data across multiple medications, ages, and disease processes to improve medication efficacy and safety in difficult to study populations (Fig. 1).

2. Methods/design

2.1. Objectives

The primary objective of OPTIC is to characterize the PK and PD of drugs of interest (DOI) administered per routine care to critically ill children with heart disease to uncover age- and disease-related effects using population PK/PD modelling and simulation. DOI specific exploratory objectives include defining clinical endpoints and characterizing safety using outcomes such as pain scores and laboratory values, respectively.

2.2. Study design

The OPTIC platform consists of prospective, open-label, non-randomized studies characterizing the PK/PD of multiple DOIs administered per routine care to critically ill children with heart disease in the pediatric cardiac ICU using opportunistic (obtained at the time of a routine collection) and scavenged (leftover after routine collection) biospecimen samples including whole blood, plasma, urine, peritoneal fluid, and cerebrospinal fluid. Planned enrollment is up to 2000 patients across up to 20 DOIs. OPTIC consists of a general protocol, informed consent form (ICF), and assent form for children >12 years, which is approved by the Duke IRB. The ICF is available as a hard copy or electronically, via a QR code, that directly links to a Research Electronic Data Capture (REDCap) database. Each DOI is added to the protocol as an appendix with drug-specific inclusion and exclusion criteria, sample size, PK/PD sampling scheme, biological specimen of interest matrix, and outcomes of interest, and may be submitted to the IRB separately as an addendum without change to the protocol or ICF (Fig. 2). For the first IRB submission, three commonly used drugs, one respiratory and two analgesics, were selected to be studied. The use of a general protocol and ICF allow for streamlined addition of extra DOIs without recreating the main study structure.

Parents and/or children are identified through the EHR and approached for enrollment if the child meets inclusion/exclusion criteria and is receiving at least one DOI per routine care. One general ICF is signed allowing for collection of opportunistic or scavenged biospecimens. There is an opt-in section (selected by 55% of approached patients to date) that allows for collection of biospecimens from indwelling lines at non-routine collection times. An optimal PK/PD sampling scheme relative to drug dosing interval is provided in the DOI appendix for these patients, but samples collected at other times are not considered protocol deviations. An example is shown in Table 2. A maximum of 10 samples (~0.1–0.5 mL each) can be collected per study period of 180 days and samples may be collected for multiple DOIs without another ICF. Parents and/or children may be re-consented for the same trial if still hospitalized after 180 days or re-admitted in the future.

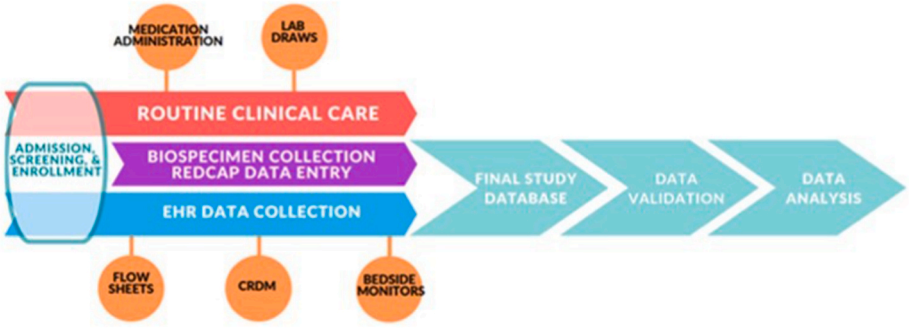

Fig. 1. OPTIC Work Flow
Work flow of the OPTIC study from admission, screening, and enrollment through data analysis. OPTIC = Opportunistic PK/PD Trial in Critically Ill Children with Heart Disease.

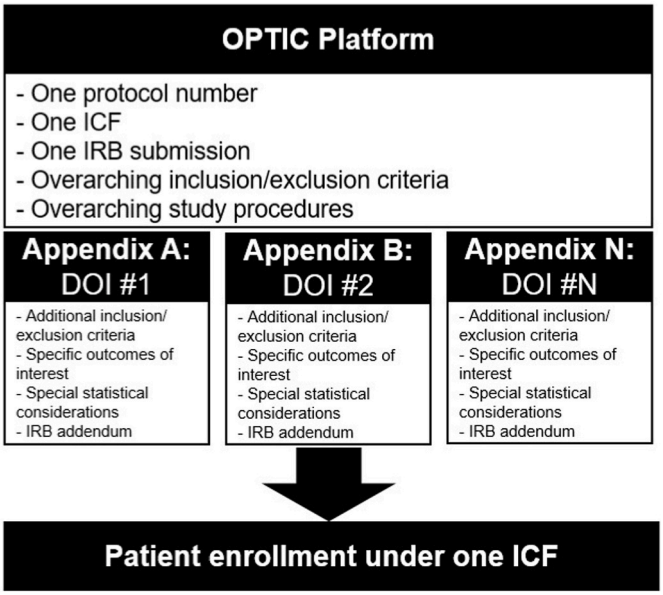

Fig. 2. OPTIC Protocol Structure
OPTIC platform protocol structure. ICF = informed consent form; IRB = institutional review board; DOI = drug of interest; OPTIC = Opportunistic PK/PD Trial in Critically Ill Children with Heart Disease.

Table 2
Example of ideal pharmacokinetic sampling scheme for a drug dosed as a single dose.

Sample Number	Time (Hours) after Single Dose
Sample #1	0[a]
Sample #2	<2
Sample #3	2–<6
Sample #4	6–<12
Sample #5	12–<24
Sample #6	24–<48
Sample #7	48–96

[a] For intravenous drug, time 0 = end of infusion; collect sample after flush ends.

2.3. Patient population

Inclusion criteria are any child <21 years of age admitted to the pediatric cardiac ICU receiving a DOI per routine care. Exclusion criteria are any condition which would make the participant, in the opinion of the investigator, unsuitable for the study. Each DOI has a target population based on age and route of administration. Within 12 months, 56 children were enrolled and 309 samples were collected across the three drugs at a single site. Multiple children received multiple DOIs and had samples collected for each.

2.4. Bioanalytic sample analysis

Opportunistic blood samples, or those collected at non-routine lab draw times, are collected in ethylenediaminetetraacetic acid (EDTA) tubes from the bedside nurse by the study team. Samples are then immediately centrifuged at 4 °C for 10 min at 2000 g. Plasma from centrifuged samples is aliquoted into cryovials, labeled, and stored at −80 °C. Scavenged blood samples are stored in EDTA tubes at 4 °C in the clinical laboratory per standard of care prior to collection by the study team. These samples are then centrifuged at 4 °C for 10 min at 2000 g, aliquoted, labeled, and stored at −80 °C.

Urine samples are collected from a urine collection bag, cotton balls in a patient's diaper, or from the metered collection column of an indwelling catheter. Samples are aliquoted into cryovials, labeled, and stored at −80 °C. Other biospecimens collected per standard of care are also aliquoted into cryovials, labeled, and stored at −80 °C.

Frozen biospecimen samples are shipped to a central, Clinical Laboratory Improvement Amendments (CLIA)-certified lab for preselected drug concentration, biomarker, and metabolite quantification. In the first year of the study, 71 samples for one DOI were shipped to our central laboratory and successfully quantitated using a validated enzyme multiplied immunoassay.

2.5. Data sources

Study data are prospectively collected and managed using four data sources as shown in Table 3. PK sample collection data and enrollment date are manually entered in REDCap [19,20]. The Duke Clinical Research Data Mart provides access to curated and characterized patient data, including demographics, the medication administration record, and lab values, that can be downloaded directly [21]. Flowsheets include documentation by nurses and respiratory therapists and are extracted directly from the EHR. Vital sign data from the bedside monitors are downloaded directly from the monitor and include near continuous patient hemodynamic data. All data are exported as *.csv* files and compiled using the software R (version 3.2.0 or later; Vienna, Austria) and RStudio (version 0.99.442 or later; RStudio, Boston, MA) to create drug-specific analysis datasets.

2.6. Data validation

Ensuring data consistency is critical to the success of OPTIC. Upon completion of the first DOI dataset, we performed a manual verification for all patients. This included entering key variables (e.g., medication administration date, time, and dose of the first dose of study drug; dosing weight recorded for the first dose of study drug; laboratory values at 0400 on the first postoperative day; and mean heart rate from 0300 to 0500 on the first postoperative day) directly from the EHR into REDCap and manually comparing these data to the automatic data extraction. This step was successful: 100% of medication administration times and doses, 94% of dosing weights, 100% of laboratory values, and 100% of vital signs were concordant, which confirmed the accuracy of the data sources. For subsequent DOIs, we will not repeat this step, but we will continue to assess for data consistency. Our data sources overlap in some

Table 3
Data sources utilized by OPTIC.

Data Source	Data Components
REDCap	Demographics (date of birth, race, ethnicity, sex, name, subject ID, MRN) Enrollment date PK sampling (DOI, sample type, collection date/time, freeze date/time, accession number)
CRDM	Demographics (name, MRN, date of birth, race, ethnicity, sex, date of death) Medications (date/time, route, dose) Labs (date/time, value) Admission/discharge date/time Diagnoses Procedures
Flowsheets	Nurse scoring systems (e.g. Withdrawal Assessment Tool (WAT) score) Height/weight Vital signs Lines and tubes
Bedside monitors	Vital signs (heart rate and rhythm, blood pressure, central venous pressure, respiratory rate, oxygen saturations)

CRDM = Clinical Research Data Mart; DOI = drug of interest; MRN = medical record number; OPTIC = Opportunistic PK/PD Trial In Critically Ill Children with Heart Disease; REDCap = Research Electronic Data Capture; WAT = withdrawal assessment tool.

data components (i.e., birth date, weight), providing an opportunity to compare multiple entries across data sources. If data from different sources are discrepant, then there will be a manual check in the EHR prior to deciding from which data source to extract.

2.7. Sample size considerations

Due to the paucity of preliminary PK data on the drugs under study, formal sample size calculations were not performed. Sample size calculations will be performed for each DOI in accordance with FDA guidance, targeting 90% confidence intervals for PK parameters of interest with desired precision between 60% and 140% of the geometric mean estimate [22–24].

2.8. Statistical analysis

Children who receive at least one dose of a DOI and have at least two PK samples will be included in the final analysis. The number of subjects who complete the study and those who are not included in the analysis will be summarized. Statistics will be reported per DOI. Descriptive statistics such as number of observations, mean, median, 95% confidence interval, standard deviation, standard error, minimum, and maximum will be presented for continuous variables, and counts, proportions, and/or percentages will be presented for discrete variables.

2.9. PK analysis

Clinical and demographic data from the EHR will be merged with the biospecimen information to create a PK dataset for each DOI. Since a sparse sampling scheme is employed, population PK methodologies will be used to analyze the PK data using NONMEM (version 6.1 or later; Icon PLC, Dublin, Ireland). Covariate analysis will examine the correlation between model parameters with demographic and clinical factors and co-administered medications. Appropriate covariates will be incorporated into the model using a standard forward-addition ($p < 0.05$, change in objective function value [ΔOFV] >3.84) and backward-elimination ($p < 0.01$, ΔOFV >6.63) technique. We will evaluate model fit per FDA guidance using prediction (goodness of fit) and simulation-based (prediction-corrected visual predictive checks) diagnostics. As appropriate for each DOI, the following PK parameters will be estimated: systemic clearance, volume of distribution, maximum concentration, time to achieve maximum concentration, absorption rate constant, elimination rate constant, half-life, and area under the curve. We will perform sensitivity analyses to ensure scavenged and opportunistic sample concentrations are consistent.

2.10. Exploratory PD analyses

PD markers of interest will be defined *a priori* if there are data available in the literature. Otherwise, exploratory PD endpoints will be investigated. Relationships between observed and population PK model-predicted exposures and PD markers will be explored graphically and described using summary statistics. Population PK/PD modeling may be performed based on results of the exploratory PD analysis. As appropriate, various PD structural models (e.g., indirect response or effect compartment) may be evaluated using estimated (combined fit) or fixed (stepwise approach) plasma concentrations of the DOI. Covariates on PD parameters may be evaluated based on biologic plausibility and a stepwise selection approach as described for PK modeling above.

2.11. Dosing simulations

Based on results from the population PK model and the exploratory PD analyses, we will conduct dosing simulations to characterize exposures shown to be associated with safety or efficacy endpoints. Data from dosing simulations will be used to guide dosing recommendations in our population.

3. Discussion

OPTIC is a minimal-risk, minimal-burden point-of-care trial that will efficiently facilitate the execution of PK, PD, efficacy, and safety analyses in vulnerable, difficult-to-study populations across drugs and disease processes. Prior studies have shown EHR-based real-world data and scavenged samples can be successfully leveraged in small studies, but no pediatric point-of-care trials have been designed to capitalize on the amount of data collected per routine care [6,7,12,13,15,16]. Critically ill children with heart disease are an ideal population in which to implement and evaluate the feasibility of this trial design as routine care already necessitates multiple medications, frequent lab draws, and detailed vital sign monitoring and EHR documentation. Other pediatric population PK studies using scavenged samples have shown increased variability in those concentrations due to unstandardized storage conditions and inaccurate recording of sampling time [25,26]. OPTIC addresses these limitations by ensuring sample stability at various storage conditions through testing by our central laboratory and standardizing storage conditions in the protocol for all samples from all sample methods. Additionally, while the time recorded in the EHR may slightly deviate from the actual sample collection time, the workflow in our ICU requires that the nurse scan the sample label at the bedside of the patient. Using this sample collection time allows OPTIC to continue to maximize efficiency and minimize burden with only slight discrepancies (seconds to minutes) that we do not anticipate will affect the validity or reliability of the population PK model. OPTIC also has built in flexibility to ensure adequate numbers of samples in each sampling window; since patients may be enrolled in multiple drugs, we are able to track the number of samples collected in each sampling window for each drug and target sampling windows in drugs with fewer samples.

We have had success in many aspects in the early stages of implementing OPTIC that overcome the barriers of traditional PK/PD studies. Enrollment has been successful with the majority of approached parents recognizing the minimal risk design to the study and providing consent. Our preliminary analysis demonstrates successful quantification of drug levels from small amounts of plasma scavenged from prior lab draws. We successfully collected samples during all PK sampling windows in the ideal PK sampling scheme. Multiple trainees were able to gain experience in consenting, sample collection, and data analysis through having multiple DOIs. We have successfully extracted diverse types of data from the EHR and complied them into one database, which we will validate. Once we have developed this structure, extracting the data required from enrolling more patients or developing additional DOIs will necessitate minimal additional resources, streamlining ongoing research efforts.

To date, the implementation of the first three DOIs in the pilot and validation phase of OPTIC has proven to be feasible, minimal risk, and minimal burden, though enrollment is not yet completed. We will use this point-of-care trial to characterize the PK/PD of drugs given per routine care and determine safe and efficacious drug dosing in critically ill, difficult-to-study populations. These data can help determine how age- and disease-specific factors affect drug PK/PD and the real-world evidence generated may lead to FDA label changes. In addition to meeting the primary objectives, this trial can assess the adequacy of PD endpoints, evaluate associations with PD endpoints and clinical outcomes, and inform future trials. Ultimately, this trial design can be applied to other drugs in other disease processes.

We envision this trial design expanding to other medical centers to further advance our knowledge of therapeutics in the pediatric population, particularly accounting for practice and regional differences. The ubiquity of the EHR means the data required for our PK, PD, safety, and efficacy endpoints are routinely acquired. While our analysis requires data extracted from the Duke Clinical Research Data Mart, similar clinical data warehouses are employed by several other institutions

[27–29]. One problem we anticipate as this trial design expands is consistency of data collection across institutions. This may require additional data validation steps, such as ensuring accuracy of documented times of medication delivery and sample collection, and performing sensitivity analyses with both systematic and random errors added to the administration time to evaluate the potential impact of data collection mechanism on PK assessments. Based on our experience validating data across data sources, we do not foresee this being prohibitive, and expansion and adaptation should allow for effective increased patient enrollment.

OPTIC overcomes several major hurdles that have previously limited PK, PD, safety, and efficacy trials in difficult-to-study pediatric populations. The pilot phase of OPTIC has been successful to date, and we are currently proceeding with activation of more DOIs and their associated biomarkers and endpoints. By leveraging the existing infrastructure of the EHR and routine care, OPTIC is being conducted with maximal efficiency and minimal burden. Data produced by OPTIC have the potential to be of substantial value to all investigators studying vulnerable and difficult-to-study populations.

Ethics approval and consent to participate

Informed consent will be obtained from all parents or legal guardians. The study is approved by the Duke Institutional Review Board and will be performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

ET was a major contributor in writing the manuscript. All authors substantially contributed to the design of OPTIC. All authors read and approved the final manuscript.

Authors' information (optional)

n/a.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Abbreviations List

DOI	drugs of interest
EHR	electronic health record
EMA	European Medicines Agency
FDA	Food and Drug Administration
ICF	informed consent form
ICU	intensive care unit
OPTIC	Opportunistic PK/PD Trial In Critically Ill Children with Heart Disease
PD	pharmacodynamic
PK	pharmacokinetic
REDCap	Research Electronic Data Capture
U.S.	United States

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