



Background Information

Jaeb Center for Health Research

Introduction

The Jaeb Center for Health Research (JCHR) is a nonprofit clinical trial coordinating center/contract research organization (CRO) founded in 1993. With a staff of approximately 130, JCHR occupies roughly 33,000 square feet of self-contained, restricted-access office space in Tampa, Florida. JCHR established an organizational structure with centralized resources (e.g., information technology, quality assurance, regulatory, institutional review board [IRB], contracts, accounting), including standard operating procedures that support all JCHR projects, and a robust methodology for the coordination of multi-center randomized trials and epidemiologic studies.

JCHR continually strives to improve its methods and remain on the cutting edge of technology in its clinical studies. There is strong collaboration among JCHR's projects and staff with sharing of both scientific and operational knowledge. This infrastructure is applied to a broad scope of projects, from single-center or small multi-center (3-5 clinical sites) projects, up to and including large multi-center projects involving more than 100 clinical sites.

Being an independent entity (i.e., not part of an academic institution) enables JCHR to initiate new projects quickly by adding new staff if needed; implementing agreements with industry; implementing subcontracts with participating centers; and procuring the required equipment and supplies for each study. In almost 30 years of operation, JCHR has established subcontracts with more than 500 entities for the conduct of its projects. Many of its projects were funded through single grants or contracts to JCHR, with JCHR providing funds through subcontracts to participating clinical sites and other entities—often on a per-participant or milestone basis. JCHR does not charge indirect costs on subcontracts with clinical sites and other entities.

The JCHR IRB has served as a central IRB for multi-center studies for more than 20 years, providing IRB coverage and oversight for U.S. clinical sites—both private practices and institutions. The JCHR IRB currently provides coverage for more than 300 sites, and among these, has reliance agreements for IRB coverage with more than 125 universities and other institutions (the remainder being private practices without an IRB).

JCHR is successful in enforcing a requirement that clinical sites in the studies it coordinates use the central IRB. The IRB is part of the JCHR Human Research Protection Program, accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). The JCHR IRB is extremely efficient and recognizes the importance of a smooth, rapid IRB process so that IRB coverage does not delay study startup timelines.

JCHR considers its ability to achieve effective collaboration among researchers to be one of its strengths. In building collaborative networks, JCHR has been successful in bringing together academic institutions as well as private practices to work together for a common goal. This arrangement broadens the scope of patients for clinical studies that not only enhances recruitment but increases generalizability of the study results. It also has benefit in the dissemination of study results to impact clinical practice at the conclusion of a study.

Studies Coordinated by JCHR

JCHR has coordinated more than 100 multi-center studies in the last 27 years. The studies have included a wide range of study designs, including randomized parallel group trials, crossover trials, and factorial design trials; cohort and case-control epidemiologic studies; inpatient clinical research center experimental studies; neuro-imaging studies; and registries. Although the studies are primarily U.S.-focused, several studies have included clinical sites outside of the U.S., including Canada, England, Germany, France, Italy, Slovenia, Finland, and Israel.

Many studies coordinated by JCHR have involved an investigational drug or device. JCHR has served as the IND/IDE holder, fulfilling sponsor regulatory requirements for more than 20 studies. Additionally, JCHR has extensive involvement in other IND/IDE studies in which it was the CRO and a company was the IND/IDE holder. Some of the investigations included fulfilling regulatory requirements in Canada, the EU, and other countries where there were clinical sites.

JCHR was the CRO for the following phase 3/pivotal studies that have led to product approval:

- **Glucagon nasal powder:** *JCHR was the CRO for the two pivotal studies used to obtain FDA approval. The drug was developed by Locemia, Inc. At the conclusion of the pivotal studies, the drug was sold to Eli Lilly, which obtained FDA approval and markets the drug as Baqsimi.*
- **Tandem t:slim X2 insulin pump with Basal IQ technology:** *JCHR was the CRO for Tandem Diabetes Care's pivotal trial, which eventually led to FDA approval of this device.*

- **Tandem t:slim X2 insulin pump with Control IQ technology:** *JCHR was the CRO for two pivotal trials in adults/adolescents and in pediatrics that resulted in FDA approval of this automated insulin delivery system.*

Eye Disease Studies Experience

JCHR was involved in eye disease projects since its inception in 1993, related to JCHR's founder, Roy W. Beck, M.D., PhD, being an ophthalmologist. The initial study coordinated by JCHR was the Longitudinal Optic Neuritis Study, an extension of the Optic Neuritis Treatment Trial funded by the National Eye Institute (NEI) that evaluated risk factors in patients with optic neuritis for the development of multiple sclerosis. This was followed by the Herpetic Eye Disease Study (HEDS) funded by the NEI, which conducted several RCTs and an epidemiologic risk-factor study in the 1990s. HEDS had 74 clinical sites, including both university-based and community-based sites. Thereafter, incorporating community-based sites collaborating with academic-based sites in clinical trials became a major focus of many JCHR projects. Additional subsequent cornea studies included the Cornea Donor Study, the Cornea Preservation Time Study, and starting in 2021, the Diabetes Endothelial Keratoplasty Study, all funded by the NEI.

Most of the other eye disease studies coordinated by JCHR were part of three networks. The Pediatric Eye Disease Investigator Group (PEDIG), funded by the NEI, was established in 1998. Since its inception, the network has conducted more than 50 studies involving more than 100 community-based or academic-based clinical sites with representation from both ophthalmology and optometry. The DRCR Retina Network was established in 2020 and, similar to PEDIG, is a collaboration of more than 100 community-based and academic-based clinical sites. The network has conducted more than 35 studies which initially focused solely on studies of diabetic retinopathy but subsequently expanded to include all retina diseases. Established in 2016, the Foundation Fighting Blindness Consortium is funded by the Foundation Fighting Blindness and consists of more than 35 centers specializing in the treatment of rare retinal diseases. The network is conducting both longitudinal natural history studies and clinical trials.

Diabetes Studies Experience

JCHR has coordinated adult and pediatric studies in diabetes—both type 1 diabetes (T1D) and type 2 diabetes (T2D)—since 2001. The company's involvement began with the NIH-funded Diabetes Research in Children Network (DirecNet), which conducted multiple studies in different aspects of T1D over more than 10 years. Studies that involved participants with established or new-onset T1D, as well as type 2 diabetes, include the landmark JDRF CGM RCT and multiple continuous glucose monitoring

(CGM) and artificial pancreas studies funded by the NIH, Helmsley Charitable Trust, JDRF, and industry.

Diabetes Device Studies

JCHR has experience with multiple generations of CGM devices since 2001 and artificial pancreas systems since 2008. In addition to the aforementioned JDRF CGM RCT, JCHR coordinated the following CGM RCTs in adults with type 1 diabetes: REPLACE-BG and WISDM funded by the Helmsley Trust and JDRF, and the following CGM RCTs in adults funded by Dexcom: DIAMOND in type 1 diabetes, DIAMOND in T2D, and MOBILE in T2D. Additionally, JCHR has coordinated numerous artificial pancreas studies for established or new-onset T1D, including being the CRO for the Tandem Basal-IQ and Control-IQ studies that led to FDA approval, and the pivotal insulin-only Bionic Pancreas randomized trial. To support device studies, JCHR has developed data management processes for the uploading and cleaning of CGM data, as well as analytic methods, including a validated SAS macro to calculate common CGM metrics.

Diabetes Drug Studies

JCHR has coordinated studies involving metformin for overweight adolescents and young adults with T1D and insulin resistance; low-dose glucagon for the treatment of mild or impending hypoglycemia and for hypoglycemia-prevention during exercise (in collaboration with Xeris Pharmaceuticals); nasal glucagon as rescue therapy for severe hypoglycemia (in collaboration with Locemia and with Lilly); and verapamil for new-onset T1D.

Diabetes Registries

JCHR launched the Pediatric Diabetes Consortium (PDC) in 2009, which initially was a collaboration among seven U.S. pediatric diabetes centers funded jointly by three companies: Novo Nordisk, Boehringer Ingelheim, and Takeda. Over a two-year period, the PDC established a registry of more than 1,000 youth with newly diagnosed T1D who were followed prospectively from the time of onset of T1D. Later, the PDC expanded to 47 pediatric diabetes centers and established a pediatric T2D registry.

In 2010, JCHR established the T1D Exchange Clinic Network funded by the Leona M. and Harry B. Helmsley Charitable Trust, with 80 adult and pediatric diabetes centers in the U.S. The T1D Exchange Clinic Network included a registry of approximately 35,000 adults and children with T1D, building upon the structure established for the PDC registry. Registry data were utilized to define the state of T1D in the United States and led to innumerable oft-cited publications, as well as national and international presentations. Collaborations were established with registries from other countries.

In addition to the registry, the T1D Exchange Clinic Network conducted multiple randomized trials and epidemiologic studies. The pivotal studies evaluating a nasal glucagon preparation that formed the basis for FDA approval of the drug were conducted within the T1D Exchange network. Also executed within the T1D Exchange network: the aforementioned randomized trial evaluating metformin in overweight adolescents and young adults with T1D and insulin resistance and a series of studies evaluating low-dose glucagon for the management of hypoglycemia and prevention of exercise-induced hypoglycemia. Enrollment for many of these studies was achieved rapidly by recruiting participants from the registry, using contact information provided by participants who indicated a desire for contact regarding potential studies.

Experience with Virtual Diabetes Studies

JCHR has led three projects, funded by the Helmsley Charitable Trust, that were conducted completely outside of clinics with direct contact with study participants. All data collection occurred through the completion of forms by participants on the JCHR website; participant uploading of device data; and home collection of capillary blood samples for HbA1c measurement by a central laboratory (a method JCHR validated in a study comparing HbA1c measured from capillary samples with venous samples). The studies included a prospective observation study of the Loop do-it-yourself artificial pancreas system which included more than 1,000 participants; the collection of insulin, glucose, and meal data before, during, and after exercise with meal photographs analyzed at a central reading center; and a study in which CGM is initiated virtually and training is provided by certified diabetes educators. Additionally, within the T1D Exchange registry, numerous observational studies were conducted through direct contact with registry participants by having the participants complete online questionnaires.

Information Technology

A study database and website are the backbone supporting many coordinating center functions and the conduct of each study. JCHR has a central core team of Informational Technology (IT) staff who support all JCHR projects. Each JCHR project has an assigned data manager and Web application developer who is responsible for the database and website developed for the project. Additionally, JCHR has a data standards specialist who assists the project IT team in the use of common data elements (CDEs). Standard Operating Procedure (SOP) documents cover all aspects of IT-related processes and procedures that JCHR staff follow. JCHR's computing environment is compliant with FDA regulations including 21 CFR Part 11. All production systems are housed offsite in a certified datacenter managed by Flexential. Backup and redundancy procedures

cover all JCHR servers, including having georedundancy for all systems at a second Flexential location in Nashville TN (in the event of a hurricane or other natural disaster) using cloud storage. Extensive security measures are in place to protect the servers from unauthorized internal access as well as external intrusion. Study websites are password protected and restricted to users authorized by the CC to gain access through a multilevel authorization structure. A full audit trail is maintained for all changes made to records in a study database.

Databases

JCHR uses MS SQL Server as its core database. An established database structure is used for all protocols to provide consistency across various types of studies. New databases are created for a project from a template, and standard procedures are followed for table and field attributes and for maintaining database documentation. JCHR maintains several levels of database servers: *development*, *staging*, *training*, *production*, and *replication*. The *development* database server contains test/simulated data and is used for development and review purposes. All facets of website application development are maintained as consistently as possible across projects and protocols to support quality control measures, as well as enhance user accessibility and promote the reuse of code.

Software Development

The Microsoft platform is used for application development of new web applications, including MS SQL Server, T-SQL, and .NET. Site content and layout for a protocol are standardized by selecting required elements from lists of tasks and website features compiled from the implementation of multiple and varied studies. For each new project, these lists are reviewed to identify development required for the project.

Clinical Trial Management System

JCHR has developed a 21CFR Part 11-compliant clinical trials website, which includes its electronic data capture (EDC) system and many project management and study-related functions. The website is customized to include the specific functionality required for a study, building upon existing applications JCHR has already built. Site content and layout for a protocol are standardized by selecting required elements from lists of tasks and website features compiled from the implementation of multiple and varied studies. Task development progress is tracked using management system software. New tasks and modifications to existing tasks are added and assigned to a primary Web application developer who has overall responsibility for ensuring the task is completed by the due date.

During development, a management tool is used to monitor progress of tasks being developed. JCHR development processes follow an industry standard Waterfall methodology, governed by the Software Development Life Cycle (SDLC) process consisting of several phases: design, development, review, unit testing, staging (quality assurance testing), production, system validation, and maintenance.

The following list includes core functionality available for all JCHR projects:

- Electronic case report forms (CRFs)
- Randomization
- Editing CRFs
- Viewing/printing CRFs
- Viewing and printing reports such as patient rosters, visit schedules, past-due visits, adverse events, device issues, inventory tracking, recruitment, retention, protocol deviations
- Electronic informed consent process
- Participant completion of patient-reported outcome surveys
- Study document repository (e.g., protocol, procedures manual, participant information sheets, numbered memos)
- Electronic site-specific regulatory binder setup in SharePoint
- Electronic document sign-off (e.g., investigator acknowledgements of protocol and other documents)
- Laboratory shipment/tracking system
- Adverse event reporting
- Medical monitor review
- Device tracking/accountability system
- Supply ordering/shipments/accountability
- Study participant tracking, including an application for entering the study appointment date and for the study monitor to communicate directly with the study coordinator
- Protocol review and querying – review of cross-form checks and possible deviations that allow more real-time remote monitoring and communication with sites
- Electronic sign-off on CRFs, edits, and protocol deviations
- Secure file uploading capabilities (using Amazon Cloud to facilitate the process and file storage)
- Customized menus that follow the protocol and procedures

JCHR has a library of existing validated eCRFs that can be used in a study, which reduces development time and costs. These include the following:

- Informed consent form signing documentation, assent, and consent addendum forms
- Visit Information – visit date and the investigator and coordinator responsible for visit
- Medications – includes a look-up table to the RxNorm database that loads as a medication is typed
- Pre-existing Medical Conditions – includes a look-up table to the MedDRA database that loads conditions as site personnel type
- Adverse Events – includes a look-up table to the MedDRA database that loads conditions as site personnel type
- Device Deficiency or Issue
- Device Download Information
- Physical Exam– height, weight, vital signs, and physical exam assessment
- Pregnancy Test Results and Pregnancy Notification forms
- General Visit Comments
- Socioeconomic Information
- Participant Final Status

Additionally, the following diabetes-specific validated eCRFs are available for use in a study:

- Insulin Types and Administration
- Hypoglycemia Event Information
- Diabetic Ketoacidosis or Severe Hyperglycemia Event Information
- Diabetes Screening – includes common baseline data collected for diabetes studies such as sex, race/ethnicity, diabetes diagnosis date and/or age at diagnosis of diabetes, insulin delivery method, total daily basal and bolus insulin, CGM use, history of severe hypoglycemia, and diabetic ketoacidosis events
- Diabetes Follow-up Treatment – updates for insulin delivery modality, insulin dosing, and self-monitoring of blood glucose
- Diabetes Tanner Staging Assessment
- Diabetes Local HbA1c – HbA1c collection date, method, and value

These validated eCRFs may be quickly implemented for a study with additional study-specific custom eCRFs developed as needed. In addition, JCHR has a library of previously developed patient-reported outcome questionnaires.

There are many SOPs that govern the Information Technology databases and software application development – available upon request.

Quality Assurance and Regulatory Compliance

JCHR's Chief Research Compliance Officer oversees the Human Research Protection Program (HRPP); privacy requirements including the Health Insurance Portability and Accountability Act (HIPAA) and the European Union's General Data Protection Regulation (GDPR); conflicts of interest; and regulatory requirements particularly with respect to the FDA. This JCHR office also manages JCHR's SOPs used for staff training in good clinical practice (GCP) and other research-related areas. JCHR's monitoring SOPs describe the elements of a study monitoring plan and the documents required for each study that describe how compliance is achieved with regulatory, privacy, and other requirements. As part of the certification process of clinical sites, JCHR's project team requires that investigators and other key personnel have documented GCP training, and if not, provides resources for training completion. The JCHR project team's monitoring of a study focuses on GCP adherence at clinical sites and any other entities involved in study data creation. A list of relevant JCHR SOPs is available upon request.

Monitoring

Daily monitoring is conducted by a JCHR protocol monitor who undergoes an internal certification process before being able to fulfill this role, with the assistance of a research assistant under the direction of a JCHR study director. Monitoring typically follows a risk-based monitoring approach in accordance with the FDA guidance "Oversight of Clinical Investigations—A Risk Based Approach to Monitoring." (<https://www.fda.gov/downloads/Drugs/Guidances/UCM269919.pdf>).

Monitoring procedures for a study build upon the foundation of existing JCHR monitoring procedures and documentation. As much as possible, monitoring is done in real-time or near real-time. The JCHR eCRF system includes customized data checks to avoid missing required fields and flag out-of-range or internally inconsistent data entries to allow corrections before submission to the database. For data added to the database, a customized application is run weekly to identify potential protocol deviations and data issues. Study Protocol Monitors communicate with the sites through a Web application to resolve issues or record protocol deviations. A third level of data evaluation is performed on accumulated data monthly by a study statistician.

This action further evaluates the data for missing or inconsistent information. All CRF data edits are made by the clinical site using a Web application that records in the database the old value, new value, date/time of change, who made the change, and the reason for the change for a complete audit trail.

A separate document is created to complement the monitoring plan that lists each data collection variable for the study. It describes if there were any quality control checks on the variable and whether the check occurred during data entry, during manual edit review, during automated protocol review, and/or during end-of-study (or end-of-phase) closeout.

The JCHR study team typically reviews data monitoring reports with the sponsor and/or an oversight committee monthly. The reports generally include participant accrual by site, participant retention by site, visit completion by site, and protocol deviations by site. Additionally, these reports are available to sponsors in real time on the study website.

Elements of a risk-based monitoring plan generally include the following:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of IRB coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- Listing of key data fields with respect to intensity of monitoring
- Communications with site staff
- Participant retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

The risk-based monitoring plan focuses on pre-defined key, or critical, fields for the most intensive monitoring. Key data fields are considered “high risk” in that they could affect data integrity, participant informed consent, eligibility, study intervention (drug/device), efficacy, or safety. The following data generally are considered key or critical data for monitoring:

- Informed consent form completion
- All eligibility (inclusion and exclusion) criteria
- Study drug or device use and discontinuation

- Adverse events
- Device deficiencies (for device studies)
- Key laboratory values
- Patient reported outcome survey completion

A customized program is run weekly to confirm adherence with the protocol and check data consistencies that cannot be identified on data entry. The study protocol monitor conducts the reviews, communicates with the site, and determines if a deviation is warranted. If a form is edited, a protocol review is repeated to identify issues or deviations that resulted from the edit.

Each anticipated type of protocol deviation is predefined as major or minor. Major deviations are evaluated as to whether they meet criteria for IRB reporting. All deviations are signed off by the site coordinator and site investigator.

The following list cites monitoring reports generally reviewed weekly at JCHR:

- Adverse events (to verify that the event is consistent with protocol reporting requirements)
- Device issues
- Forms pending data entry
- ICF discrepancies and missing forms
- Past-due visits
- Pending device data
- Protocol deviations
- Forms and protocol deviations pending investigator sign-off
- Any study-specific monitoring reports

Feedback to sites on the quality of their data is performed in multiple ways and described below.

- Upon review of the entered eCRFs, the site coordinator is contacted regarding any data inconsistencies and discrepancies. If a major issue is identified or consistent issues occur, the PI is notified of the issue and a phone call may be scheduled to discuss the problem.
- Each site has access to real-time monitoring reports available on the study website. Weekly emails are automatically sent for issues such as past-due visits, pending labs, etc.

- For each protocol deviation at the site, the principal investigator and the investigator and coordinator responsible for the visit (at which the deviation occurred) are required to sign off on the protocol deviation. Sign-off occurs through the study website. Investigators and coordinators are reminded of pending sign-offs through weekly automated emails. In addition, a count of pending items is displayed when the individual logs onto the study website.

In the past, periodic onsite visits were made to each site for the auditing of records. Since the onset of the COVID-19 pandemic, JCHR project teams have conducted remote site monitoring visits instead of in-person visits, which have proved successful and productive. It is anticipated that JCHR's future approach will be a hybrid of onsite and remote monitoring visits.

Safety Monitoring

JCHR has an SOP for safety monitoring, including the role of the Medical Monitor. The JCHR website has customized eCRFs for sites to report adverse events and, where applicable, device issues. There also is a Medical Monitor review application for adverse events and device issues. The application includes a querying tool for the Medical Monitor to communicate with the clinical site so that all communications are recorded. The Medical Monitor has access to view all CRF data for a participant on the website as needed (e.g., pre-existing medical conditions, medications, prior history). The applications allow the Medical Monitor to re-code adverse events and adjudicate device issues with the clinical center. Adverse events and pre-existing conditions are coded using the MedDRA classification system.

JCHR works closely with the study sponsor on reporting serious adverse events (SAEs), serious unexpected adverse reactions (SUSARs), and unanticipated adverse device effects (UADEs) to fulfill regulatory requirements.

For studies with an independent safety committee/data safety monitoring board, JCHR provides coordination and administrative support, as well as producing the safety and analytic reports for the committee to review.

Statistical Analyses

JCHR has approximately 20 statisticians, with about 10 working solely on diabetes studies. Each study has an assigned statistician who is supervised by one of two senior statisticians. The senior statisticians have many years of experience in the analysis of data from diabetes studies.

Statisticians are involved in studies from the initiation of protocol development, assisting with study design issues, and writing the statistical analysis plan, through the end of the study when final analyses are conducted for manuscripts and

presentations. JCHR statisticians become knowledgeable in the disease area in which they are working, which is a significant asset in communicating with clinicians and in determining the optimal statistical approach to address in an analysis objective. Statistical analysis plans are generally complex and involve not only the analytic methods but also the approach for managing multiplicity, missing data, and sensitivity analyses. Hierarchical approaches for addressing multiple outcomes are often used. The analysis plans and analyses of JCHR statisticians have successfully withstood the scrutiny of FDA statistical reviewers, as well as the statistical reviewers of top-tier journals.

The publication of study results and presentations at national and international meetings is a major objective of each study, particularly in top-tier journals. In the last five years, JCHR Coordinating Center staff have authored more than 250 publications in peer-reviewed journals, with many in top-tier journals including four in the New England Journal of Medicine, six in JAMA, two in Lancet, and two in Annals of Internal Medicine.