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Challenges in conducting multicenter, multidisciplinary longitudinal studies in children with chronic conditions

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Abstract

Objectives—Conducting longitudinal, multi-center, multidisciplinary research for individuals with chronic conditions can be challenging. Despite careful planning, investigative teams must adapt to foreseen and unforeseen problems. Our objective is to identify challenges encountered and solutions sought in a recently completed observational, longitudinal study of youth with cleft lip and palate as well as their caregivers.

Methods—Data for analysis were derived from a six-year, multi-center, prospective, longitudinal study of youth with cleft conducted from 2009–2015 that examined oral health-related quality of life and other related clinical observations over time in youth who had cleft-related surgery compared to those who did not. Youth and their caregivers participating in this study were followed at one of six geographically diverse, multidisciplinary cleft treatment centers in the United States.

Results—Establishing effective communication, ensuring protocol adherence, safeguarding data quality, recognizing and managing differences across sites, maximizing participant retention, dealing with study personnel turnover, and balancing/addressing clinical and research tasks were particularly exigent issues that arose over the course of the study. Attending to process, ongoing communication within and across sites, and investigator and clinician commitment and flexibility were required to achieve the stated aims of the research.

Conclusion—Studying children with cleft and their caregivers over time created both foreseen and unforeseen challenges. Solutions to these challenges are presented to aid in the design of future longitudinal research in individuals with chronic conditions.

BACKGROUND

Some scholars attest that observational research is the “next best method” to address research questions that cannot be ethically or adequately addressed by randomized controlled trials (RCTs)¹. Indeed, evidence suggests that well-designed observational studies, including prospective cohort studies, may be capable of providing analogous results to RCTs in studies that examine the relationship between risk and protective factors and health outcomes¹. Due to ethical considerations, research measuring impacts of specific, elective, and/or experimental surgical treatments on quality of life (QoL) and psychosocial and clinical outcomes for school-aged children with cleft are more appropriately studied using observational designs. Yet, little has been published on the challenges experienced while conducting a longitudinal, multi-center, observational study of youth with a chronic health condition.

The purpose of this paper is to document challenges and strategies for managing research outcomes of youth with cleft lip and/or palate (CL/P) and their caregivers based on a recently completed six-year, National Institutes of Health-funded, prospective cohort study of youth with cleft across six cleft treatment centers in the United States. While generating the largest U.S. database of this patient population to date, this study has concurrently provided important insight into foreseen and unforeseen challenges in conducting a complex, multidisciplinary longitudinal study. The goal of this commentary is to share experiences and lessons learned in conducting and managing long-term studies of children with chronic conditions in order to inform future studies of other pediatric patient populations.

STUDY DESCRIPTION AND FINDINGS

This study included a sample of English and/or Spanish-speaking children with CL/P, 7.5–18.5 years of age at baseline, who were seeking evaluations and care for craniofacial conditions at one of six geographically diverse study sites in the U.S. Children and one of their caregivers participated in the study. During the course of the study, some participating children received secondary cleft-related surgery, while others did not. Further details regarding the study protocol and procedures have been previously published^{2–6}.

Over the six-year course of the study, a total of 787 surgeries (43% of the participants) were performed across six cleft treatment centers. Approximately 90% of participants completed baseline and one follow-up visit, 60% completed the study protocol (two follow-up visits post-surgery or baseline), 15% had pending surgical recommendations, and 25% were lost to follow-up.

Prior publications from this study have included longitudinal analyses of positive (resiliency, mastery, and self-concept) and negative (depression, anxiety) components of psychosocial functioning, as well as oral health-related quality of life (OHRQoL)^{2, 5, 7, 8}. Findings

indicate that surgery for cleft lip and/or palate has an immediate negative impact on the family system (for example, relatedness and mastery), but the overall trend in family functioning improves over time³. With respect to quality of life, surgical intervention for CL/P was associated with an improvement in OHRQoL over time. However, a higher number of previous surgical interventions was also associated with lower self- and caregiver-rated OHRQoL scores². Additionally, minimally important differences (MID) for clinically meaningful change were calculated for the study sample using both the anchor-based and distribution criteria method⁴. These estimates can be used for surgeons and researchers to determine whether surgical intervention for cleft lip/palate has had a meaningful impact beyond statistical significance on patients.

CHALLENGES AND SOLUTIONS

Our study of a chronic condition population encountered a number of foreseen and unforeseen challenges that required creative problem-solving and flexibility throughout the course of the study.

Foreseen Challenge #1: Establishing effective communication

One of the greatest challenges in planning and managing a multidisciplinary, multicenter study is establishing effective communication both within and across study sites⁹.

SOLUTION—Regular communication, flexibility, and establishing a solid rapport with both study team members and participants were key components to the successful completion of this project. Ongoing communication was facilitated through biweekly conference calls for research assistants (RAs) across sites as well as monthly conference calls for site principal investigators (PIs). These calls provided group problem-solving, support for the team members, and a sense of coherence toward meeting the specific aims of the study. In later years, time was devoted to discussing results and dissemination plans including manuscript writing, authorship, and conference presentations. Finally, as per the scope of work, annual face-to-face team meetings were held in conjunction with the annual American Cleft Palate Association (ACPA) conference to update staff and clinicians about study progress and to troubleshoot recruitment, retention, or other challenges. Scheduling study meetings in conjunction with the annual ACPA conference helped defray travel costs to the granting agency as the majority of PIs and clinicians typically attended this conference. Collectively, these strategies were able to successfully mitigate communication challenges and contribute to the study's successful completion.

Foreseen Challenge #2: Protocol adherence

The complex nature of the longitudinal, multi-center study design created challenges related to protocol adherence. Due to differences in personnel across sites, similar roles could be assigned to various individuals (for example, patient coordinator, nurse, or RA).

SOLUTION—Prior to the study commencement, multidisciplinary members of the cleft palate teams (for example, psychologists, speech pathologists, etc.) created presentations that were shared with the team via video conferencing. These videos provided an

opportunity for study personnel to review the protocol and ensure calibration for various components of the research (for example, Extent of Difference ratings). Procedural strategies were used to facilitate adherence to the protocol and communication across sites. First, a Manual of Operations (MOPs) was created that outlined study procedures. The MOPs was also amended throughout the study in response to protocol changes. For example, retest data for Extent of Difference ratings (perceptions data for facial appearance, teeth, and speech) were added to the study with RAs mailing forms one week after the follow-up assessment to participants and their caregivers to complete and send back. Additionally, the site PIs had all staff complete Delegation of Responsibility Forms, which detailed the roles and duties of each individual by site. These strategies ensured study personnel across sites understood the protocol and were able to adhere to it. During years 1 and 2 of the grant period, site visits by the PI and the data manager were conducted to discuss challenges at the sites, ensure adherence to the protocol, engage in collective problem-solving, and foster rapport with the teams. Utilizing these strategies (for example, MOPs, Delegation of Responsibility Forms) allowed us to successfully mitigate the challenges associated with protocol adherence across sites.

Foreseen Challenge #3: Ensuring data quality

Based on the complex study design, ensuring data quality was paramount.

SOLUTION—Prior to study commencement, the study PI selected the study measures and met with the statisticians and database manager to review questionnaires and technical infrastructure. The statisticians reviewed the instrument test manuals to assure instrument validation and the existence of proper normative values; the database manager created forms that were readable (for example, using a large font size and contrasting colors for test items) and ready for data entry. The database design ensured that data entered were consistent and within appropriate ranges. To verify accuracy of the data entry, a separate database for a subset of data re-entry was established. The results were compared and verified for accuracy. After the study began, the database manager routinely checked for any security issues and software updates. As per best clinical practices, any change made to the database was logged with both the old and new values, the identity of the person who made the change, and when and why the change was made. The database was also designed to alert RAs when participants were due for a follow-up assessment. We found having a skilled, dedicated database manager is essential for conducting multi-center, longitudinal studies. The database design used Oracle database on the back-end with a custom web application, allowing sites to use web browser for access. This design ensured that all data were stored at a central location only and not on sites' computers. The web application was accessible only to authorized personnel associated with the study. This application was enforced by username/password authentication and role- and site-based authorization, only allowing each site access to their site's data. The interface allowed secure data entry, which was protected in transit by industry-standard encryption. All protected health information (PHI) in the back-end database was encrypted, which also provided protection at rest. The interface utilized branching logic, hiding entry fields and forms irrelevant in context. This ensured that only relevant data could be entered. For instance, the "Global Assessment of Change" form would be hidden for initial visit, and only accessible in follow-up visits. Similarly, if surgery was

not recommended for the participant, the questions about surgery details were not asked. The interface also verified the completeness and integrity of the data before they were saved, thus improving quality of the data. Involvement and input from the database manager and statisticians prior to and throughout the project ensured that the study's data were of the highest quality possible and that the specific aims could be successfully achieved.

Foreseen Challenge #4: Maximizing participant retention

Maintaining participant enrollment over time is an inherent problem in longitudinal studies.

SOLUTION—To promote and sustain participant interest, newsletters about the study were given to all participants (either via mail or at the time of their clinic appointments). Newsletters provided updates about the study and were also used to disseminate annual study findings. Participants were also sent birthday and holiday cards to foster comradery and reinforce that each site valued youths' continued participation. Anecdotally, participants reported that they valued receiving this information and felt more connected to the long-range goals of the study. A study website was also developed that explained the study aims and updated study findings. Testimonials from the participants and observations from key research team members were also shared in the newsletters and websites. In short, valuing stakeholder engagement meant we made a concerted effort to foster participant interest and promote their retention.

Another tactic, often used in some projects, is the creation of an advisory board comprised of key stakeholders. However, due to the age of the participants and the ongoing relationship between the caregivers and clinical community, such a board was not implemented in this particular study. It has been used in our other research with infants with cleft and their caregivers and may be useful in research with other pediatric patient populations, particularly when clinicians, participants, and community leaders have not had prior engagement with research. Overall, we are confident that these tactics were able to maximize participant retention to the extent possible.

Foreseen Challenge #5: Study personnel turnover

Another challenge experienced during this longitudinal study was study personnel turnover, particularly in relation to research assistants (RAs). RAs played a vital role in enrollment, data collection, and data entry throughout the study. Two sites had to replace RAs over the course of the study, and one of the sites had two turnovers in RAs. Unfortunately, the lead statistician also passed away during the course of the study, which meant time and resources were spent finding another statistician and familiarizing him with the dataset, study documentation, and codebooks. While staff changes are expected during the course of longitudinal studies, such turnover meant training the new personnel to ensure continued implementation of the study protocol.

SOLUTION—One way of dealing with team member turnover that we have successfully used in another study is to create videos and PowerPoint presentations of the study protocol, which can aid in the training of new personnel, particularly RAs. Additionally, ongoing documentation of analytic strategies, decisions, and codebooks, as well as access to the PI,

were critical to advance the new statistician's understanding and adaptation. In all, our efforts to train new study personnel were able to successfully mitigate the challenges associated with personnel turnover.

Unforeseen Challenge #1: Departure of plastic surgeon from study site

While some turnover in RAs is anticipated in a longitudinal study, the departure of principal team members is not. Unfortunately, the primary plastic surgeon at one cleft center changed locations. One of the cornerstones of cleft care is continuity and the disruption of a major service provider likely interfered with the successful execution of the site's surgical procedures. It is noteworthy that while this site hired a new plastic surgeon, it ultimately had the highest rate of postponing or patient refusal of surgical recommendations.

SOLUTION—No concrete solution was identified, other than highlighting the importance of patient-doctor trust in team care. When a senior clinician departs from a team, communicating to patients and families that the team is dedicated to continuity of care is paramount. Future research should be aware that such departures are possible. Transitioning new key team members is a particular task that requires planning, resources, and other team considerations from both the site's administration and clinicians.

Unforeseen Challenge #2: Cleft team member issues related to completing research forms

Unanticipated logistical issues were encountered as clinicians were required to add another step in their clinical practices. One such example involved speech evaluations. Many speech pathologists had difficulty completing their study-related assessments of the participants' speech in addition to their already established clinical assessment protocols and responsibilities. This problem was especially challenging in the centers' clinics, with their high patient volumes on team days, which made completing the assessment rating forms difficult.

SOLUTION—An agreed-upon solution to this problem was to have the speech pathologists digitally-record their standard research assessments. This solution eased the burden of rating the speech samples during busy clinic hours. Such challenges underscore the difficulties inherent to studying cleft care outcomes across centers. Further, RAs made site-specific arrangements to ensure specialists had their designated research clinician forms prior to the participants' clinical evaluations and when and where completed forms were to be received by the RAs for protocol consistency and timely data entry. Such prearrangements were vital as specialists (for example, surgeons) had unexpected appointments at the hospitals. These strategies successfully alleviated challenges related to completion of the research forms by cleft team members.

Unforeseen Challenge #3: Managing differences across sites

The study encountered unanticipated site differences that potentially threatened study objectives. Even though the cleft teams adhered to the ACPA Parameters of Care¹⁰, teams differed on the timing of surgeries with one site often performing surgeries (for example, secondary palatal surgeries) prior to the study enrollment age of seven. Variation also existed in treatment activism across sites. For example, only 26% of study participants at one site

had surgery compared to 54% of participants at another site. Interestingly, more procedures were actually performed overall than the study PI projected, which is generally the opposite of clinical research trials.

Participant recruitment varied more than was anticipated across sites. Despite requesting sample pool estimates from participating sites during the planning of the proposal and project, there was variability in how valid these estimates were and in how well sites were able to achieve recruitment goals, with several sites under-achieving their projected recruitment estimates. Some of this variability was due to the complexity of patients seen at some sites (for example, greater numbers of children with syndromic clefts or who had clefts in the context of multiple other congenital anomalies) which may not have been fully accounted for in the initial sample estimates. One site actually had a higher patient volume and number of surgeries than anticipated, which helped off-set the sites that under-performed. However, it is important to note that even though differences across sites created challenges, they also revealed impacts from the real world (such as site differences identified above) rather than an ideal experimental one.

SOLUTIONS—Recruitment variability at sites was addressed through annual budget adjustments for sites' participant fees and allotments for personnel at each site, thereby allowing an additional site to be added after year one. As a precaution for under-enrollment, a letter of support for a back-up site was secured prior to study initiation, which was important since most trials reportedly under-recruit¹¹. Establishing a back-up implementation plan proved to be a critical safety net to meet our targeted recruitment and power estimates. While adding a back-up site addressed low enrollment at certain sites, in hindsight, inclusion and exclusion criteria must be carefully reviewed and verified with each site PI before site enrollment estimates are calculated during the study planning phase.

Unforeseen Challenge #4: Follow-up assessments

The study was designed with the intention of assessing outcomes at participants' annual team appointments. However, in retrospect, relying on annual team appointments for follow-up proved to be unrealistic as adolescents who did not undergo surgery had little interest in annual follow-up. Further, variation also existed across sites with some children being recalled to the clinic earlier (for example, 6 month intervals) or, more commonly, later (for example, two year intervals) than a year. Participant follow-up also was deterred by site differences in patient discharge from team care despite the accepted study protocol. For example, one site dismissed patients based on age (including study participants) before they completed the study protocol. Finally, scheduling follow-up appointments for participants who did not undergo surgery at one year and two years post-baseline raised important ethical questions about the intersection of research and clinical care.

SOLUTION—To maintain adherence to the study protocol, some participants were seen for their follow-up assessments during partial or single provider visits (for example, orthodontic appointments). While this strategy helped improve the study's ability to gather follow-up data, following participants over time remained a challenge. Emphasizing commitment

across sites must be understood and accepted by each team. Discussions regarding study requirements and participant burden were conducted during the later years.

CONCLUSIONS

Conducting the largest longitudinal, multi-center, prospective study of school-aged children with cleft and their caregivers resulted in foreseen and unforeseen challenges. Although the ACPA Parameters of Care advocate measuring outcomes and cleft care requires ongoing clinical evaluations and treatment, study teams' adherence to a consistent research protocol created a perceived clinical conflict or simply a change in the norm at the team site level. In essence, when conducting clinical or community-based research, all stakeholders require careful consideration and commitment to the research goals prior to study onset. In the case of cleft care, caregivers, youth, and clinicians may perceive there to be less value and necessity of a team appointment, particularly during times when a child is in a "holding pattern" before additional surgery or treatment is indicated or recommended. These issues may result in less willingness to schedule or attend team appointments for follow-up visits. Defraying costs of care to complete research protocols may require budgetary planning by the PI for additional financial support from the research sponsor. In short, it is critical to pay careful attention to such issues when designing outcome studies and to consider other ways of obtaining valid assessments if in-person visits are not feasible. For example, using secure, online data collection systems such as Research Electronic Data Capture [REDCap]¹² and telephone interviews are worthy of consideration. Fortunately, advancements in statistical programs and methods were employed to control for time variability between follow-up participant assessments.

Categorizing some challenges as 'foreseen' and others as 'unforeseen' does not imply that one category is more or less relevant in impacting the achievement of the study goals. The fact that challenges arose at varied times throughout a project underscores the importance of communication to address problems as expeditiously as possible. As George Bernard Shaw astutely said, "The single biggest problem in communication is the illusion that it has taken place," which highlights the importance of including scheduled communication throughout the study within and across sites. To begin, it is imperative that both clinical and research team members have a collective buy-in to the project and that participation in conference calls is mandated to address site-specific and/or protocol dilemmas. The importance of clinical care for both the cleft teams and the research team may be an implicit strength that could be used to bridge the potential divide between clinical care and research outcomes. In conclusion, this paper reveals challenges experienced in conducting a longitudinal, multicenter study of children with chronic conditions and highlights the need for flexibility in study design and implementation in addressing these challenges.

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