Teaming for excellence: challenges and collaboration in the world of reproductive clinical and translational research

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To succeed in the conduct of clinical trials in reproductive medicine, teams must be trained and cultivated to collaborate and achieve a common goal. Here I share my personal experiences and lessons learned in teaming in the research setting by covering topics in time management, resource allocation, collaboration, publishing, and communication. (Fertil Steril® 2021;■:■–■. ©2021 by American Society for Reproductive Medicine.)

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It goes without saying that our lives and work in recent years have been dominated by the COVID-19 pandemic. Alongside the development of multiple vaccines for COVID-19 are some notable achievements in biomedical research. In the pursuit of an enhanced understanding of this dreaded virus, the release of Google's AlphaFold 2, the computer algorithm that can predict three-dimensional structures of proteins with atomic accuracy, is arguably the most prominent accomplishment in contemporary scientific research. The article by Jumper et al. (1) has nearly 20 coauthors, and without any doubt, there are at least 10 times as many individuals who contributed to the successful completion of this important project. Such a large-scale collaboration has now become the rule rather than the exception. If we open any issue of *Fertility and Sterility*, *Nature*, *Science*, or the *New England Journal of Medicine*, we find that all major original publications involving human subjects have multiple coauthors. Teamwork is a necessity, not just a convenience, for advancing both basic and translational biomedical research. More importantly, the concept of "teaming" is just as important when dealing with research teams as it is with clinical teams, since there are often many unique components to research collaborations. These include different laboratories, multiple clinical sites, different hospital and government officials, a stable group of senior researchers and a constant rotation of junior researchers, postdoctoral students, and clinical interns. The six core components of teaming—cognition, coordination, communication, cooperation, conflict, and coaching—are extremely important for a successful research team, and optimal execution of these concepts requires thoughtful awareness to ensure maximum communication, psychological safety, productivity, and success.

CHALLENGES OF A RESEARCH TEAM

To establish a productive research team, there are several unique challenges that must always be considered by the primary investigator.

Time. Developing and instituting a research project requires an enormous time commitment. For the academic researcher, this time may be built into the job description, but it is never enough, especially as you begin to develop and balance multiple projects. Time is even more precious if you are a clinician and research is not your primary designated role. Often, compromises must be made to ensure that adequate time is set aside to appropriately design and navigate the inception of a new project.

Funding. For any researcher, financial support is always limited and is constantly being sought. An enormous amount of effort is often spent applying

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for grants and searching for philanthropy to help keep projects moving. Often, funding is directed to a specific project or end point, whereas some monies are earmarked for the general goals of the research laboratory, giving the investigators more latitude in dispensing funds where they are needed most.

Team collaboration. Productive research, like any other team effort, depends on the motivation and expertise of its members, but also on the culture, diversity, and psychological well-being created in the laboratory. Reinforcing the laboratory's objectives yet understanding the goals and motivations of each of the team's members is critical. Dealing with outside influences, such as the National Institutes of Health (NIH), the Institutional Review Board, and others, as well as working with site investigators as part of a multicenter project, requires a primary investigator to be fluent in the "art of teaming."

Publishing. All research efforts rely on conducting experiments, generating meaningful results, and publishing these results. The initial effort that goes into designing a study appropriately, establishing authorship, and keeping people on task is often rewarded with quality research and meaningful results. Quality research not only investigates issues at hand, but also tries to anticipate questions or ideas that will occur later and be more relevant when a project is actually completed.

TEAMING WITH THE NATIONAL INSTITUTES OF HEALTH

The NIH have numerous funding mechanisms. My own "teaming" experience has been with NIH grants funded through Research Project Cooperative Agreements (U01) and Cooperative Clinical Research Cooperative Agreements (U10). These U mechanisms are cooperative agreements between the NIH and recipient institutions. There are at least two notable distinctions from some of the more common investigator-initiated mechanisms, such as the Research Project Grant Program (R01). First, these are generally requests for applications that are issued by the NIH with specific goals and overall budgets. Second, NIH program officials and/or project scientists who are the driving force for the requests for applications also participate in the daily operation of the activities and may provide real-time guidance or supervision of the studies. Multiple elements of teaming are embraced when working directly with scientists and/or officials of the NIH, including cooperation, communication, and cognition.

To expand further on the above example of cognition, I refer to the ability to understand that these governmental agencies not only have their research end points, but also have other groups looking over their shoulder to ensure that their funds are used wisely, projects are being completed, and their agenda is being completed. It is critical that they become your allies, as they usually are, and they are often embraced as key members of the team. The goals of the researcher and the NIH official are the same, and the opportunity to directly address any conflict directly with your funding source should really be seen as an opportunity to ensure consistency with the research goals and psychological safety. To have the NIH program and project officials act as advocates for our research and to partner with NIH project scientists to offer scientific and clinical direction has been one of my most rewarding experiences as the principal investigator (PI) of multiple funded projects.

Within the U mechanisms, there are critical differences among them. A major difference between U01 and U10 is that U01 is usually designed for one funding cycle, whereas U10 is open for future renewals. It is more difficult to develop productive teams when your major funding source is only guaranteed for one cycle. Diversity should always be encouraged and embraced by a research laboratory. Differences in culture, background, experience, and expertise often become vital to a laboratory's success. Diversity also comes with unique challenges. It can take time to develop technical expertise, knowledge of a research topic, and clear channels of communication and mutual respect. It takes a village to keep everyone motivated and working toward a common goal for an extended period of time. Under the U01 mechanism, a team is usually disassembled right at the moment that it reaches its maximum efficiency.

EXAMPLES OF RESEARCH TEAMING

In 2005, I had the privilege of serving as a PI for the first time, on the data management, statistics, and informatics core for the Genomic and Proteomic Network (GPN) for Preterm Birth Research (2). Although it is called a "core," it was in essence a typical data coordinating center. It was funded through U01 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The GPN consisted of three clinical centers, each led by a maternal-fetal medicine expert, a genotyping core also led by a maternal-fetal medicine expert, and my core. The Steering Committee (SC) was also led by a maternal-fetal medicine expert. One of the two NICHD program officials was again a maternal-fetal medicine expert. What was distinctly missing on the GPN team was a human geneticist who could have anticipated the need for validation studies and advised the rest of the SC members in planning and designing such studies before we exhausted our resources and time. Importantly, after realizing the importance of a validation study, the GPN investigators were able to obtain additional samples from other networks. However, our genotyping core was unable to obtain viable signals from the most promising single-nucleotide polymorphisms. When we identified a second facility to regenotype the validation samples, we found that those samples were exhausted. This missed opportunity underscores the importance of having the right experts from the outset to lead different teams and complement each other.

In 2007, my team was fortunate again to assume responsibility for the NICHD-funded Reproductive Medicine Network (RMN). From the perspective of team building and resources, it was vital to have an existing team. We had several years of experience working together. With two networks to coordinate, we had more resources and were able to hire more staff to cross-cover our activities. The RMN was funded by the U10 mechanism, which left the door

open for future funding cycles, and in fact, we successfully competed for a renewal. It was much easier to attract and motivate staff if a long-term career opportunity existed, and the quality of their contributions directly affected the chance of renewal. This, however, changed again in 2017 when the NICHD withdrew funding from the RMN, and the resources were used to create a new program. Because a successful clinical trial involves many medical, statistical, operational, and regulatory issues, it takes years for a research staff to become familiar with best practices for clinical and collaborative research. Although it is clear that the NIH's initiatives will change over time, the importance of continuity of a team can sometimes be overlooked, as a robust program such as the RMN is closed and another is initiated.

With the GPN, the goal was specific, but the hypotheses were not; we did not know in advance what genetic variants would be associated with spontaneous preterm birth. In fact, when the GPN was initiated, we did not even know what genotyping platform to use and what the predicted cost would be. In contrast, the goal of the RMN was broadly defined for improving the treatments for infertility patients, but the hypotheses were specific once we determined which clinical trials to conduct. The latter specificity was critical in our planning. With this information in hand, we were able to project how many patients were likely needed and what the budget would be for the participants. We were able to allocate reasonable resources to complete all trials. This ability to project and allocate resources was the first step in our success. By constant communication and collaboration, I was able to work with the NICHD program and project officials to ensure that the committed funds were always there.

During the first iteration of the RMN, we completed three clinical trials. The first was the Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) trial (3, 4). The Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS) trial was our second study (5, 6). Recruitment for AMIGOS proceeded much more smoothly because of the inflow of research funds from the American Recovery and Reinvestment Act, which allowed us to provide for all patients' care for unexplained infertility. Our third completed trial was a physiologic oxygen (PhOx) study. We recruited 840 couples who underwent in vitro fertilization (IVF) procedures. Our goal was to compare live birth rates with two oxygen levels (5% and 20%) in the culture conditions, and we found that the live birth rates were similar. The PhOx trial is a perfect example of the obstacles to conducting an IVF trial in the United States. Trial recruitment was completed in 2013 and the database was locked in 2014, which was 6 or 7 years after the start of the first RMN iteration. It was evident that designing an impactful and programmatic IVF study was extraordinarily difficult. Another 6 or 7 years after the trial was completed, our study remains unpublished; editors and referees felt strongly about how they practiced IVF and how they interpreted the policies on IVF-related research. None of us anticipated the degree of controversy that the translation of our results into a publication would create.

During the second iteration of the RMN, we lost some clinical sites from our first phase and added some new sites. All members of the network competed on their own merits in the second iteration and were judged to an important extent on the quality of a proposed protocol that they would lead within the network. However, like other networks, the RMN functioned as a team with protocols modified and prioritized by the SC as well as by a peer advisory board (NIH study section). Some proposals may not have been considered by the peer reviewers to have sufficient merit when they stood alone, but the investigators could have made significant contributions within a team environment and as recruitment sites for the network. The ability, commitment, and environment to support a multicenter trial should be viewed as an important factor.

A MULTICENTER APPROACH TO TEAMING

How did an RMN clinical trial proceed from conception to completion? We shall see again the importance of experience and continuity of a team. The peer review by an NIH study section largely determined the composition of the RMN and was also an important consideration in the RMN's prioritization of which trials to implement. However, the RMN advisory board provided its own independent assessment and recommendation to the NICHD and the RMN SC, with information that the NIH study section did not have, namely, the composition of the RMN team. At this point, the RMN SC voted on a list of possible protocols and determined the order for prioritization. Before the voting, every clinical PI had the opportunity to make an appeal for his or her concept proposal in terms of its potential impact, his or her own experience, and the protocol's feasibility. Once a protocol was selected, the data coordinating center worked closely with the NICHD project scientist and the SC, especially the chair and the lead PI, to fully develop the study. Naturally, the lead PI had the highest stake. The presence of the NICHD project scientist, the SC chair, and the data coordinating center PI is vital to the ethical and daily operation of the RMN team. The relative impartiality of these leaders ensured that all members of the RMN worked toward the common goal, had an opportunity to voice their concerns and advocate for their research, and had the resources to fully implement their project within the confines of a dedicated team.

TEAMING ACROSS INTERNATIONAL BOUNDARIES

Designing and coordinating research in China, as with many other international collaborations, is associated with a cloud of "untrustworthiness." This was particularly true for the first clinical trial in which I was involved in evaluating the role of acupuncture in improving the live birth rate among the patient population with polycystic ovary syndrome (7). A great teaming method that I used was to communicate openly with the Chinese team regarding these challenges and address anxiety about dropouts, protocol deviations, and adverse events. I felt that these concerns would be reduced if the study design and protocol were as flawless as we could make them. Engaging my colleagues from China in discussion, giving them a forum to voice their concerns, and reminding them that even for the most experienced PIs and well-established research networks, it is almost impossible to run a trial as

perfectly as it was designed were important elements of our success. Once the research team realized these concerns and discussed them openly, it was easy for everyone to create protocols that would minimize scrutiny. Reporting of adverse events would be encouraged and transparent, allowing each researcher to understand this and avoid any issues moving forward. My previous experiences allowed me to coach them in a productive way. In the end, the quality of our study, even though we showed no improvement with acupuncture treatment, was received quite favorably. We successfully fostered a "teaming" approach to research with colleagues in China that helped to reduce researcher apprehension and eliminate a potential underlying perception of mistrust.

When we were provided with the opportunity to study acupuncture in China, there were undeniable interests in wanting acupuncture to have a positive effect. This profound bias required a great deal of coaching in order to educate my research colleagues on the impact a large study can have on clinical care. How do you handle the potential risk that a traditional Chinese medicine technique such as acupuncture (with a long-held belief of benefit) may not turn out to be beneficial? Sharing with all research teams that a good-quality study design will provide good-quality answers—even if the answers are not what they want to hear—is an essential part of science. This clear message helped to reduce some of their concerns. Publishing a negative study of a time-honored Chinese medicine technique in a high-impact journal helped to reinforce the quality of the study (7), even though it received less press than another acupuncture study that showed a positive effect for other diseases.

There were advantages to performing a clinical trial in China that no investigators could even dream of in the United States. First, the qualifications of all research personnel were uniformly high. The selected clinicians and faculty members were familiar with the unique patient populations and treatments. There was no need to hire a research staff who might be completely naïve to a trial and no need to provide salary lines, given the way the Chinese systems expect their physicians to support research. From the PIs to the data managers, all were certified physicians and specialists. For this reason, most of the team meetings took place on weekends and in big cities so that the research would not interfere with their regular care of patients. Second, whereas recruitment is among the greatest challenges of any clinical trial in the United States, the large pool of patients in China significantly ameliorated this headache, though it still took longer than expected to recruit the sample size.

A TEAM APPROACH TO AUTHORSHIP

Building a team is not easy. Maintaining a team is not any easier, especially when ambitious contributors are eager for authorship status and first author spots are limited. There is usually one "first author" and one "corresponding author," no matter how many individuals are involved and no matter how many of them play critical roles. Authorship, and especially first authorship, is important to career advancement. The ability to reward the contributions within a large number of coauthors is essential to the long-term success of a team. It is always best to be up front in such collaborative or multicenter projects regarding a clear and preferably written authorship policy specifying the criteria for authorship (as opposed to acknowledgment) and authorship order for publications. In the academic world, there has been a push to recognize that research is truly a "team" effort by allowing co-first and co-last authors. This shift in author recognition demonstrates that those most intimately involved in research recognize its fundamentally collaborative nature.

CONCLUSION

Building the right team from the start will make future work easier and increase the likelihood of success and productivity. With the right team, it is easier to plan and make informative and programmatic decisions. Even with generous support from NIH funding, the level of financial support is never enough. The ability to prioritize a wide spectrum of work with fixed budgets and follow through on our agreements and commitments is essential to forming a collegial and trust-based rapport within a relatively large team. Even with the right team and sensible planning, early recruitment is always difficult. Plans and strategies will inevitably change during the course of a study, and the research team must be adaptable to this change, especially in recruiting patients.

A thoughtful and careful plan can be a blueprint for success, and new techniques and standards of clinical care naturally evolve, which can be frustrating. Anticipating these possibilities and being transparent will help us to be better prepared and remain motivated. Working with staff who are attentive and motivated, ensuring small successes to overcome "research fatigue" while working toward the final, common goal, and realizing that a highly functioning team takes time to develop are key for any researcher.

The most successful team is the one with the greatest continuity. The deliverables of teamwork ultimately depend on preserving the integrity of research and eliminating an appearance of conflict of interest. The general concepts of teaming that hold true for clinical teams also are crucial for effective research units, and perhaps even more so because of the need to work with team members who are at multiple sites, internationally based, or perhaps have other competing interests, such as government agencies. Cognition, coordination, communication, cooperation, conflict, and coaching (mentoring) are all vital aspects of a successful research team.

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