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## September 2019

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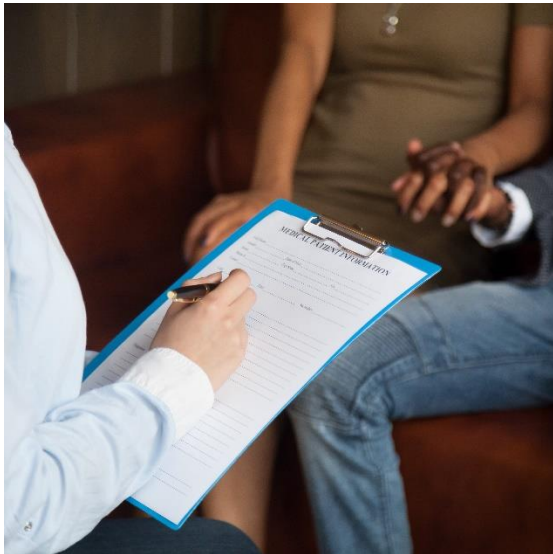
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PEER REVIEWED

## **Perspectives on Successes and Challenges in the Recruitment and Retention of Pregnant Women in a Research Study**

Amy Rider, RN; Christine Aubry, RN; Sara Moyer, RN; Patricia Kinser, PhD



Pregnant women have historically been excluded from clinical trial research, given their former “vulnerable population” status and in consideration of potential impacts to the developing fetus. However, the National Institutes of Health (NIH) and the NIH Office of Research on Women’s Health have called for more expansive research to address areas of high clinical need and to promote evidence-based clinical practice related to pregnancy. {1}

To promote an inclusive research environment and to enhance the rigor of future studies, it is essential to discuss the multiple challenges that may arise regarding recruitment and retention of pregnant women in clinical trials, and to share perspectives on successes and failures in individual studies.

In this paper, we focus on the importance of consistency, flexibility, and compassion by the research nurse/clinical research coordinator. We present perspectives on challenges and successes regarding recruitment and retention of pregnant women in a longitudinal pilot study designed to evaluate the feasibility, acceptability, and preliminary effects of a self-management intervention for depressive symptoms. {2} We also discuss successes and “lessons learned” within the context of recruitment methods, study design, and retention strategies.

## **Consistency, Flexibility, and Compassion in Recruitment Methods**

To engage in effective recruitment, we found that the process of building trusted relationships {3,4} was at the heart of our study's success. Collaboration with community stakeholders and clinic staff and establishing trusted relationships are steps that take much effort prior to the initiation of the study, but when done well, contribute to success in both recruitment and retention. {3,5}

In our study, we built effective relationships in several ways. First, we capitalized upon contacts within our academic institution (Virginia Commonwealth University), from healthcare providers to registration staff, to provide layers of access as entry points to successful recruitment. {6}

For example, speaking with the local director of CenteringPregnancy® Care (a group prenatal care approach of the Centering Healthcare Institute) led to a meeting with the clinical coordinator of the ambulatory care center; their collegial relationship paved the way for research staff to have access to vacant rooms, print-outs of the daily schedule, and computers. The director also allowed research staff to speak to prenatal care groups as an active recruitment strategy.

As another example, a key contact within the academic institution was the social worker for the high-risk obstetrics clinic, with whom our principal investigator (PI) and head research nurse met at a local café in the community prior to the start of the study. Meeting outside the busy clinic setting meant that the social worker could get to know the study details and staff in an unrushed environment and feel confident about making study referrals.

Second, our study team used both active and passive recruitment methods, with the goal of reducing recruitment bias and facilitating access to a diverse community population. {7}

Although passive methods, including flyers, Facebook posts, and e-mails to listservs, were successful for reaching many interested individuals, we found that active recruitment was essential, and the only way to effectively do so was to develop relationships with clinic staff.

For example, active recruitment in busy clinic waiting rooms can be challenging, so orientation to the “ins and outs” of clinic operations was critical. By meeting with clinic nurses at staff meetings, study research nurses gained credibility and learned how to minimize intrusions on

clinic operations; thanks to this credibility, clinic staffers offered use of vacant rooms and computers and referred patients to the study. These informal orientations allowed study research nurses to feel less intrusive while recruiting in the clinic waiting rooms. By cultivating mutual respect between the clinic and research nurses, the two could co-exist working toward equally important missions of the academic institution: research and clinical care.{4,6}

Research suggests that engagement of healthcare providers is a critical component for recruitment. Previous studies have suggested that participants are more likely to sign up for research if it has been recommended by their healthcare provider.{7,8} Similarly, engaging in informal networking with clinicians and having regular presence at key events has been found to be key to the successful recruitment of pregnant women.{9}

In our study, the clinics of midwives, obstetricians, psychologists, and primary care providers were targeted as access points because it was clear to us that it was critical for healthcare providers to have confidence in, and a connection with, the research nurses in order to make referrals. Further, our presence at local clinician conferences, Grand Rounds in the academic health system, and local conferences were important aspects of recruitment.

For example, we secured a booth at a conference of the local Association of Certified Nurse Midwives chapter, during which we were able to communicate with midwives who showed enthusiastic interest and actively referred interested individuals. It was important that we maintained active staffing at this event, rather than simply placing materials at an unstaffed booth; this is consistent with previously mentioned studies{4,9} that found certain techniques to be fruitful (such as attending healthcare provider conferences) and certain techniques to be unfruitful, such as lack of staff presence at events, newspaper advertisements, and recruitment postcards. As another example, the PI talked with the academic health system's chief resident for Obstetrics/Gynecology after Grand Rounds, who acted as a "champion" of the study—providing brochures for fellow obstetricians and who subsequently sent us several participant referrals.{6}

Two additional important recruitment methods were "flyering" and thinking "outside of the box." First, although it is a time-consuming practice, "flyering" involves spreading flyers/ brochures in multiple venues throughout a community, from churches to busy restaurants.{10}

An important aspect of “flyering” is to maintain professionalism while posting flyers: this includes asking permission to post when necessary and following the rules of the bulletin board. In addition, because of our commitment to reaching women of all socioeconomic backgrounds, flyers were delivered to health department resource centers in lower income communities; during this time, study research nurses briefly educated health department staff about the study.

Second, in order to increase recruitment numbers, study research nurses accessed “outside the box” entry points such as car-seat installation sessions at a large retail store, yard-sale events at local low-income housing developments, childbirth education classes and doula sessions at a local library, and “electronic flyering” via social media. Although recruitment was minimally successful at several of these sites, important connections were established with community members in attendance. In addition, fruitful social media sources included individual doulas’ Facebook pages, new mom/baby Facebook pages, and university-wide e-mail blasts.

A key lesson learned from the experiences described above is that in-person visits, rather than e-mails or phone calls, to recruitment sites will enhance success in connecting with clinicians about the study. Engaging the “gate-keepers” of offices (typically the receptionist or clinic manager) was essential and is consistent with other research{5}; an effective manner to pique interest is for the research nurse to briefly state how the study goal overlaps with the mission of the practice and that it is run by a reputable academic institution. For future success, we recommend building upon a network of interdisciplinary connections to enable scheduled meetings with office managers and clinicians.

Another lesson learned is that low-income housing developments may be rewarding targets for recruiters of future studies wishing to access a diverse population. Many housing developments have onsite childcare, which may address the common barrier of time and need for childcare.

In our study, we made a successful connection with a social worker at a local low-income housing development who arranged space in the community center for intervention delivery. Unfortunately, the individual was unable to identify pregnant residents. Nonetheless, this setting should be considered as an important option for future studies, given previous researchers’ successful experiences with low-income housing community partnerships.{ 11 }

## **Consistency, Flexibility, and Compassion in Study Design**

Striking a balance of consistency, compassion, and flexibility in the study design was important in its implementation. {12} Within a context of respect for the initial pilot study design, our team collaborated with Virginia Commonwealth University's Institutional Review Board (IRB) and our Data and Safety Monitoring Board (DSMB) to implement small changes to the recruitment and retention plan to afford a more compassionate, flexible approach to participants' needs, as supported by previous work. {6}

Creating ease for depressed, pregnant woman study participants became a goal for recruitment and retention. With the creative and flexible thinking of the study PI, we were able to make subtle changes that not only increased recruitment numbers, but also met the needs of the women. {12}

One example of a change to the study design intended to enhance flexibility for participants involved obtaining IRB and DSMB approval to allow participants a choice of in-person or phone-based baseline study visit. This was in response to our realization of the added burdens of potential participants' anxiety/anhedonia and their concerns with parking, directions, and childcare. For anyone who preferred an in-person visit but who lacked childcare at the last minute, study research nurses demonstrated flexibility by allowing the participant to bring her child to that visit.

A second IRB-approved change in study design addressed a need for active recruitment techniques. By seeking a waiver of consent through the IRB, we were able to conduct a basic medical record review prior to approaching potential participants in clinic waiting rooms. With this active recruitment approach, no information was documented about the individual prior to enrollment in the study, but the processes for potential participants who were already deemed potentially eligible were streamlined. Similarly, this prevented any potentially distressing situations for women in the waiting room who were experiencing a fetal loss or other major pregnancy complications. {13}

## **Consistency, Flexibility, and Compassion in Retention**

As a key aspect of the research endeavor, retention of participants required careful planning with efforts to maintain consistency, flexibility, and compassion. Clearly, establishing trust between the research team and participants is important. {3,5,9} Compassionate communication between study staff and participants was essential to keeping study participants engaged and encouraged during the 12-week intervention.

Consistent with other research studies, personalized and non-judgmental communication led to participants stating that they felt cared for and motivated to complete the intervention. {6,11,14} In our study, we conceptualized this in several ways; for example, the first study visit involved a brief, motivational interviewing session during which the research nurse left time for participants to talk about their depressive symptoms. A simple statement to participants (e.g., “I am so sorry that you have been dealing with this”) led some to report that no one had ever acknowledged the difficulties of their symptoms and others stated they felt the study environment was a safe space. Similarly, study research nurses checked in frequently with participants (weekly by phone or e-mail) for data collection and to monitor for adverse events, and weekly in-person at the intervention site.

Another aspect of successful retention was the wise and non-judging personality of the intervention instructor. Participant after participant reported through qualitative interviews that much of the success of the study was due to the compassionate personal qualities of this research team member.

A final aspect of retention involved the use of gift cards as IRB-approved compensation to participants at each data collection study visit (\$25 per study visit). This financial compensation proved to be important to many participants.

Lessons were learned regarding retention of participants with communication and transportation limitations:

- First, one difficulty during the study was keeping in touch with several participants, all of whom who had a lower socioeconomic status. They encountered problems having enough minutes on their mobile phones and/or lack of reliable wireless access to text or talk and/or with frequent changes to phone numbers. Creativity proved to be key in order to keep these individuals in the study; for example, a particularly complex participant had a social worker who was affiliated with the academic healthcare system. With permission of this participant, the research nurse and social worker coordinated communication and study visit information. As another example, a Google voice account was used to send/receive text messages to and from eligible participants.
- Second, transportation was a common concern for several participants. In response, our research nurse developed a working relationship with the director of a perinatal health community agency; through this collaboration, the agency organized a van to transport interested women to the study visits.

### **Discussion: Thoughts for Future Studies**

In reviewing the literature and following up on our “lessons learned,” we propose that future studies could benefit from the following strategies:

- Map the research team’s network of academic, public, and private organizations with overlapping goals related to perinatal health early in the project timeline; recognize that the most fruitful partners for recruitment are those with whom the research team has a previously established connection.
- Identify influential individuals within the healthcare community who may serve as “champions” for the study, demonstrating their strong belief in the study goals when communicating with patients and colleagues.
- Chart out a plan for a mix of active (e.g., screening and recruitment in waiting rooms) vs. passive (e.g., flyering, social media) recruitment to help enhance diversity of participants and ensure expeditious recruitment.
- Demonstrate early flexibility in research design to minimize burden to participants, while communicating with appropriate ethical/regulatory bodies.



- Consider methods to meet the needs of individuals for whom issues with technology, childcare, and transportation might limit their ability to participate.
- Convey professionalism and give an empathetic, respectful, and knowledgeable voice to the study when advertising its availability.
- Finally, and most importantly, demonstrate consistency, flexibility, and compassion in all decisions and communications regarding study recruitment and retention processes.

## Conclusion

Locating productive recruitment entry points, fostering relationships, and allowing for flexibility in a study's design can help bridge the gap when recruitment is a challenge. Through thoughtful relationships with key academic and community providers, effective recruitment can be achieved.

Understanding the nuances of the clinical setting will help research nurses gain trust from clinic staff and secure access to eligible individuals. Flexibility around study design can prevent additional burdens to the pregnant participant.

At the heart of successful recruitment and retention of pregnant women is consistent and compassionate attention from study research nurses.

## References

1. Blehar MC, Spong C, Grady C, et al. 2013. Enrolling pregnant women: issues in clinical research. *Women's Health Issues* 23(1):e39–45.
2. Kinser P, Moyer S, Mazzeo S, et al. 2019 (in press). Protocol for pilot study on self-management of depressive symptoms in pregnancy. *Nursing Research*.
3. Blaisdell LL, Zellner JA, King AA, et al. 2016. The national children's study: recruitment outcomes using an enhanced household-based approach. *Pediatrics* 137(s4), 219–30.
4. Jessiman WC. 2013. 'To be honest, I haven't even thought about it'—recruitment in small-scale, qualitative research in primary care. *Nurse Researcher* 21(2):18–23.
5. Coleman-Phox K, Laraia BA, Adler N, et al. 2013. Recruitment and retention of pregnant women for a behavioral intervention: lessons from the maternal adiposity, metabolism, and stress (MAMAS) study. *Preventing Chronic Disease* 10(2):120096.
6. Goff SL, Youssef Y, Pekow PS, et al. 2016. Successful strategies for practice-based recruitment of racial and ethnic minority pregnant women in a randomized controlled trial: the IDEAS for a healthy baby study. *J Racial Eth Hlth Disp* 3(4):731–7.
7. Maghera A, Kahlke P, Lau A, et al. 2014. You are how you recruit: a cohort and

- randomized controlled trial of recruitment strategies. *BMC Medl Res Meth* 27(14):111.
8. Sutton EF, Cain LE, Vallo PM, et al. 2017. Strategies for successful recruitment of pregnant patients into clinical trials. *Obst & Gyn* 129(3):554–9.
  9. Webster, GM, Teschke K, Janssen PA. 2012. Recruitment of healthy first-trimester pregnant women: lessons from the chemicals, health, and pregnancy study (CHirP). *Mat Child Hlth J* 16(2):430–8.
  10. Choi J, Lee J, Vittinghoff E, et al. 2016. mHealth physical activity intervention: a randomized pilot study in physically inactive pregnant women. *Mat Child Hlth J* 20(5):1091–101.
  11. Spadola CE, Rottapel R, Khandpur N, et al. 2017. Enhancing yoga participation: a qualitative investigation of barriers and facilitators to yoga among predominantly racial/ethnic minority, low-income adults. *Compl Thrp Clin Pract* 29:97–104.
  12. Cartagena D, Noorthoek A, Wagner S, et al. 2012. Family-centered care and nursing research. *Newborn Infant Nurs Revs* 12(3):118–9.
  13. Lapato DM, Moyer S, Olivares E, et al. 2018. Prospective longitudinal study of the pregnancy DNA methylome—United States pregnancy, race, environment, genes (PREG) study. *BMJ Open* 8(5):e019721.
  14. Carpenter RE, Emery SJ, Rassi D, et al. 2016. Recruitment of pregnant women to an exercise-intervention study. *J Obstcs Gyn* 36(2):200–7.

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PEER REVIEWED

## **Established Safety Profiles Allow for a Gene Therapy Boom and Streamlining of Regulatory Oversight**

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Once thought of as being pursued only in the realm of science fiction or under highly experimental conditions, the science of gene therapy is now considered to be well understood, and the field is thriving.

Gene therapy research involves delivering engineered genetic material to humans with the goal of compensating for genetic mutations, conferring the capability to produce potentially therapeutic substances, or eliciting immune responses to fight disease.

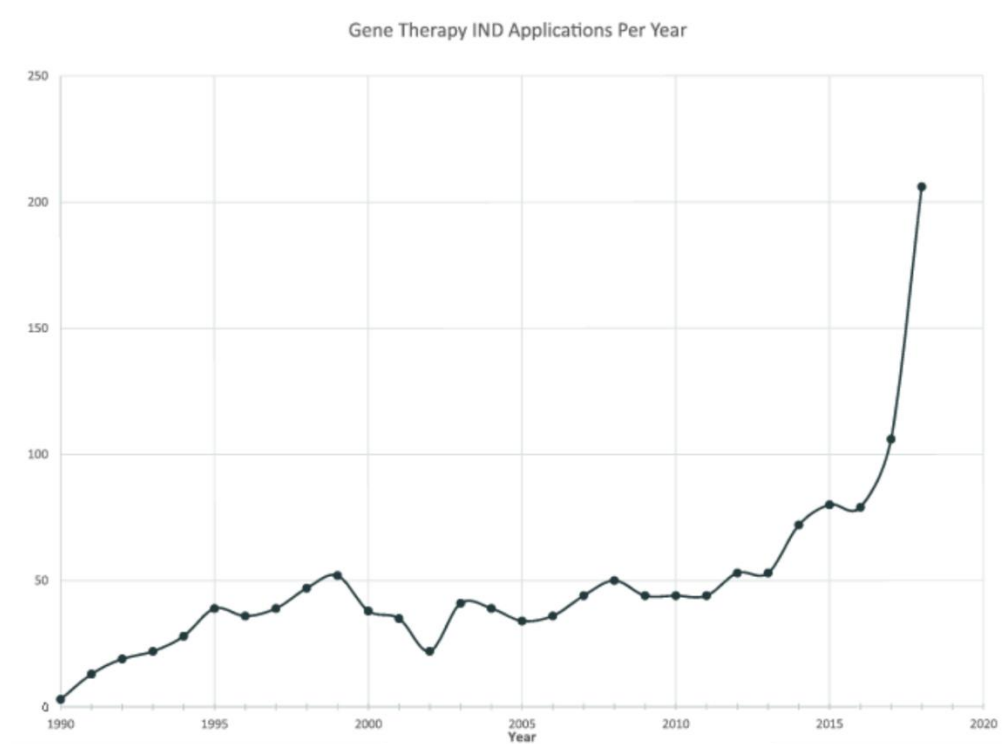
As of the writing of this article, to date, more than 2,900 gene therapy studies have been initiated worldwide. {1} Searching ClinicalTrials.gov for the keywords “gene therapy” results in more than 3,800 studies, with more than 1,000 of them currently recruiting or enrolling research subjects. {2}

The gene therapy field overcame several hurdles to reach its current state. High-profile serious adverse events have been reported over the years, including the tragic death of Jesse Gelsinger in 1999 and leukemia in children with life-threatening immune deficiencies (i.e., severe combined immune deficiency [SCID] and chronic granulomatous disease [CGD]). {3–6} These incidents

occurred at the turn of the century and led to a decade of intensive study, redesign and safety testing of gene therapy technology. {7–10}

During this period, the U.S. Food and Drug Administration (FDA) issued various guidance documents regarding the manufacture of gene therapy products, design of clinical trials, and long-term follow up for certain types of investigational products for gene therapy. {11} As the field focused on reassessing safety, the number of investigational new drug applications (INDs) received by FDA for gene therapy products has grown exponentially from 1995 to 2010 (see Figure 1). {12}

**Figure 1: Gene Therapy IND Applications Submitted Per Year**



*Data adapted with permission from Peter Marks, Director, FDA Center for Biologics Evaluation and Research (CBER). {12}*

Since 2011, the field has regained confidence in the safety of gene therapy technology, and the number of gene therapy product INDs received by FDA has been steadily climbing; 2018 marked an all-time high number of IND applications (206), almost doubling the previous all-time high achieved in 2017 (106).

The surge in research has also led to approvals (see Table 1). FDA issued its first approval of a product containing engineered genetic material (i.e., recombinant DNA) in 2015 and has since issued six more approvals, with the most recent dated May 24, 2019. With 291 gene therapy studies currently in Phase III, several more gene therapy products will likely be considered for approval in the coming years.

**Table 1: FDA Approvals of Gene Therapy Products**

<b>Product Name</b>	<b>Manufacturer</b>	<b>Indication</b>	<b>Engineered Genetic Material</b>	<b>FDA Approval Date</b>
IMLYGIC	Amgen	Melanoma	Herpes simplex virus 1 based oncolytic therapy	October 2015
VAXCHORA	PaxVax	Cholera vaccine (serogroup O1)	Live, attenuated, orally administered <i>V. cholerae</i> bacteria, cholera toxin A gene (ctxA) deleted	June 2016
KYMRIAH	Novartis	B Cell Acute Lymphoblastic Leukemia	Chimeric Antigen Receptor (CAR) T Cells, engineered with a retrovirus vector	August 2017
YESCARTA	Kite (Gilead)	Non Hodgkins Lymphoma	Chimeric Antigen Receptor (CAR) T Cells, engineered with a retrovirus vector	October 2017

LUXTURNA	Spark Therapeutics	Retinitis Pigmentosa	Adeno associated virus (AAV) vector delivering the RPE65 gene	December 2017
DENGVAXIA	Sanofi Pasteur	Dengue serotypes 1-4	Tetravalent dengue vaccine based on the Yellow fever 17D204 vaccine strain	May 2019
ZOLGENSMA	Novartis	Spinal muscular atrophy	Adeno associated virus (AAV) vector delivering the <i>SMN1</i> gene	May 2019

With the increasing number of late-phase gene therapy studies and continued growth of the field, it's important for clinical research professionals to familiarize themselves with the prospects, risks, and regulatory requirements for conducting gene therapy research.

### **Areas of Gene Therapy Research**

Approximately two-thirds of gene therapy studies are in the field of oncology.<sup>{ 1 }</sup> With the aging Baby Boomer demographic, demand for advancements in oncology and availability of research subjects for clinical trials are likely to increase.

Common areas of oncology gene therapy research include cancer vaccines, engineered immune cells targeting cancer, and oncolytics (the use of viruses that selectively reproduce in and kill cancer cells while sparing normal, healthy cells). High-profile immunotherapies, such as chimeric antigen receptor (CAR) T cells, utilize genetic engineering to reprogram white blood cells (i.e., T cells) to specifically target cancer cells. CAR T cells have been especially successful in treating B cell malignancies in cases of resistant or refractory disease.

The second most common area of gene therapy research (11.5% of reported studies) applies to monogenic diseases.<sup>{ 1 }</sup> While diseases caused by single gene mutations are rare, they represent low-hanging fruit from a technical perspective, as current technology offers a wealth of techniques for correcting single gene mutations. Examples of such diseases are listed in Table 2.

**Table 2: Examples of Monogenic Diseases**

<b>Disease</b>	<b>Description</b>
Retinitis pigmentosa	An inherited form of night blindness in children that progresses to complete blindness by adolescence.
Severe Combined Immune Deficiency (SCID)	Famously characterized by the movie <i>The Boy in The Bubble</i> , is a disease preventing bone marrow stem cells from developing into white blood cells leaving the host immune compromised.
Chronic Granulomatous Disease (CGD)	Causes impaired antimicrobial activity in phagocytic cells leading to immune deficiency and granuloma formation at sites of infection.
Cystic fibrosis (CF)	A progressive disease leading to persistent lung infections, limiting ability to breathe as well as causing digestive problems.
Hemophilia A and Hemophilia B	A bleeding disorder caused by a lack of blood clotting factor VIII and IX, respectively.
Severe sickle cell disease	Red blood cells contort into a sickle shape and die prematurely causing anemia and blockage of vasculature.

The third most common type of research (6.3% of reported studies) occurs in the field of infectious diseases. {1} Genetic engineering allows new avenues for development and manufacture of vaccines. FDA has already approved vaccines containing engineered genetic material to protect against cholera and dengue virus infections. Genetically engineered Ebola vaccines are undergoing evaluation in the current outbreak in the Democratic Republic of the Congo, with promising early results. {13–14}

## **Managing Risks Associated with Genetic Engineering and Gene Therapy Research**

Most clinical researchers are familiar with the regulatory requirements pertaining to the FDA phases of research, as well as with institutional review board (IRB) review. Gene therapy studies may require additional review to assess the risks associated with the engineered genetic material, especially as the technology frequently utilizes genetically engineered viruses to deliver genetic information into target cells. Viral infection involves the transfer of the virus' genetic material to host cells, making viruses ideal tools for gene transfer—once the viral genes responsible for viral replication and disease are removed. While genetically modified viruses have a greater safety profile than the naturally occurring unmodified variety, they remain infectious and capable of posing risks.

National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) provide the standard for oversight of research involving genetic engineering and gene therapy.<sup>{ 15 }</sup> NIH Guidelines are promulgated by the NIH Office of Science Policy (OSP) and call for local oversight at the research site by institutional biosafety committees (IBCs) that report to the NIH OSP. IBCs are charged with protecting study personnel, the community, and the environment from exposure to engineered genetic material. An IBC may also advise the IRB to aid in assessing risks to the study subjects.

The requirement for IBC review applies to gene therapy research at sites that are receiving funding from the NIH or that have ever participated in NIH-funded research. Sponsors or sites that have received any NIH funding are obligated to comply with IBC review regardless of whether the funding is associated with the gene therapy study. Studies and sites completely independent of NIH funding may still require IBC review if the research and development that led to the investigational product was funded by NIH. Even if there are truly zero NIH funds involved, IBC review is considered a best practice: [NIH Guidelines](#) state that “individuals, corporations, and institutions not otherwise covered by the NIH Guidelines are encouraged to adhere to the standards and procedures set forth” in the Guidelines (Section IV-D-1).

IBCs are composed of at least five members, including at least two unaffiliated community members, who collectively possess the expertise to assess the risks associated with proposed



research projects. IBC review involves assessing the risks associated with the genetically modified investigational product, as well as the adequacy of a facility's safety practices and training intended for use of the investigational product at the site.

The IBC ensures the site has adequate incident reporting and response plans in place to address potential occupational exposures, spills, or environmental releases of the investigational product. The IBC may review informed consents and other research subject training materials to mitigate possible risks to casual or close contacts in the community. Reviewing the site's plans for disposal of the investigational product and associated biomedical waste allows the IBC to ensure environmental protection.

Because they are charged with protecting the local community and environment, IBCs are locally based at the research site and can only oversee research at that location. For the sake of efficiency, however, local IBC meetings can be centrally coordinated and synchronized, with each IBC remaining responsible for local review.

Pharmaceutical companies and contract research organizations conducting multisite clinical trials may benefit from efficiencies provided by centrally administered IBC reviews, utilizing a model similar to central IRB reviews. NIH refers to such review bodies as externally administered IBCs and allows sites to utilize them as long as the IBCs are registered with the NIH OSP as representing the individual sites at the time the review is performed. NIH allows sites to register multiple IBCs, so an academic institution with an existing IBC focused on preclinical research in the laboratory setting may choose to utilize an externally administered IBC for review of clinical trials and industry-sponsored research.

At a single meeting, the centrally administered IBCs can conduct reviews for multiple sites participating in a single study, as long as the required local representatives are present at the meeting and separate minutes are recorded for each site. This approach streamlines the process for submission and review, providing a single point of contact for submissions as well as harmonized forms, policies, and procedures across sites.

IBC run by institutions may have set monthly or quarterly meeting schedules, and can insert IBC review as a "blocking review" (i.e., the institution's IRB will not accept a protocol for

review until the IBC has issued its approval). Centralized IBCs, in contrast, often convene “on demand,” which eliminates the practices of submission deadlines and standing meeting schedules, and results in turnaround times measured in days instead of weeks or months. For example, in 2019 the central IBC service provided by Advarra, a commercial research compliance organization, has averaged turnaround times of 7.1 business days (N = 40 studies) from submission to review for National Cancer Institute–designated cancer centers. These centers previously experienced turnaround times of up to three to four months when working with their locally administered IBCs.

### **Evolving Federal Oversight for Genetic Engineering and Gene Therapy Research**

NIH Guidelines have relied on advisory committees to review emerging research and advise the NIH Director regarding policy matters.<sup>{16}</sup> The role of this advisory committee has evolved over time.

In the 1980s, the ability to transfer engineered genetic material into humans was completely new to the clinical setting. Review of gene therapy studies was included in the responsibilities of the NIH Recombinant DNA Advisory Committee (RAC), which created the first set of requirements for review of gene therapy research in 1985.

Over time, FDA became increasingly involved with review of gene therapy studies and, in 1991, issued its own guidance document regarding review of gene therapy studies. By 1995, FDA and NIH agreed FDA would assume primary responsibility for review of gene therapy studies, with NIH and FDA jointly determining which studies required RAC review. The NIH Guidelines were revised in 2016 to require the IRB and IBC at the initial site conducting a gene therapy study to determine whether to recommend RAC review. This recommendation was based on the novelty of the science and whether the risks or possible toxicities were difficult to ascertain.

The latest version of the NIH Guidelines (issued on April 25, 2019) removes the requirements for IRB and IBC RAC determination, as well as protocol registration and reporting requirements to the NIH OSP. These requirements were deemed to be duplicative with the level of oversight currently provided by FDA as well as the IRB and IBC. As the RAC no longer reviews

individual clinical trials, the role of the RAC was revised to focus on the “scientific, safety, and ethical issues associated with new and emerging biotechnologies.”{17}

To further emphasize this more general role, the RAC has been renamed the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC). The committee’s amended charter charges it with advising the NIH Director “on matters related to the conduct and oversight of research involving emerging technologies in biomedical science....”{18}

As the committee no longer reviews large volumes of gene therapy studies, the NExTRAC can now focus on emerging biotechnology requiring the focus of a national panel of experts. Many issues are likely on the horizon for the NExTRAC, such as emerging developments in gene editing technology like CRISPR and zinc finger nucleases, especially as they pertain to clinical research. Other likely matters of future discussion include applying gene editing technology to human reproduction and environmental issues, such as gene drives and environmental release of modified mosquitos incapable of transmitting diseases.

### **FDA and the Future Oversight of Gene Therapy**

As the lead regulatory agency for review of gene therapy studies, FDA has taken a number of steps in recent years to assist in bringing gene therapy from the realm of scientific theory and research to the world of approved and licensed therapeutics for clinical use:

- FDA has issued guidance documents for the manufacture of gene therapy products, design of clinical trials, and long term follow up (see Figure 2).{11}
- The 21st Century Cures Act authorized FDA to create the Regenerative Medicine and Advanced Therapies (RMAT) designation to allow for expedited review of regenerative medicines and advanced therapies. The associated guidance issued by FDA stated the RMAT designation also applies to “...gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues.”{19}
- FDA is expanding its capabilities to review gene therapy studies in order to accommodate the growing field. In a June 2018 interview, then-FDA Commissioner Scott Gottlieb disclosed that he expects the agency to have

approved 40 gene therapies by 2022, a gargantuan number considering only four approvals had been issued at the time.<sup>{20}</sup> In a statement<sup>{21}</sup> issued in January 2019, Gottlieb and Center for Biologics Evaluation and Research Director Peter Marks mentioned plans for:

- Hiring 50 additional clinical reviewers for cell and gene therapy
- 200 IND applications for gene therapy products submitted per year by 2020
- 10 to 20 gene therapy approvals per year by 2025

### **Figure 2: FDA-Issued Gene Therapy Guidance Documents**

- Human Gene Therapy for Rare Disease
- Long Term Follow-Up After Administration of Human Gene Therapy Products
- *Disease-specific guidance:*
  - Human Gene Therapy for Retinal Disorders
  - Human Gene Therapy for Hemophilia
- Chemistry Manufacture and Control Information for Human Gene Therapy INDs
- Testing of Retroviral Vector-Based Gene Therapy Products and Patient Follow-up
- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions
- Evaluation of Devices Used with Regenerative Medicine Advanced Therapies

In their joint statement, Gottlieb and Marks write that the growth in gene therapy “...reflects a turning point in the development of these technologies and their application to human health.... It’s similar to the period marking an acceleration in the development of antibody drugs in the late 1990s, and the mainstreaming of monoclonal antibodies as the backbone of modern treatment regimens.”<sup>{21}</sup>

### **Concluding Remarks**

Once considered highly experimental and limited to early-phase studies at highly specialized research sites, the field of gene therapy has progressed to mainstream clinical research. With the

current research boom and progression into large multi-site clinical trials, clinical researchers are increasingly likely to be involved in gene therapy studies throughout their careers.

Clinical researchers should be aware of the maturation of this field and consider the opportunities it may provide to their careers and their patients. Understanding the history and fundamental technical principles of this science will allow clinical researchers to understand the capabilities and limitations of this exciting and innovative field. It is also important for clinical researchers to be familiar with the prospects, risks, and regulatory requirements to be able to safely conduct gene therapy research.

## References

1. Gene therapy clinical trials worldwide. *J Gene Med*. <https://www.wiley.com/legacy/wileychi/genmed/clinical/>
2. National Institutes of Health. ClinicalTrials.gov. [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
3. Marshall E. 1999. Gene therapy death prompts review of adenovirus vector. *Science* 286(5448):2244–5.
4. Stolberg SG. 1999. The biotech death of Jesse Gelsinger, *The New York Times Magazine*.
5. Marwick C. 2003. FDA halts gene therapy trials after leukemia case in France. *BMJ* 326.
6. Marshall E. 2002. Gene therapy with retroviruses halted. *Science*.
7. Worth T, Parker N, Herttualla S. 2013. History of gene therapy. *Gene* 525:162–9.
8. Seymore LW, Thrasher AJ. 2012. Gene therapy matures in the clinic. *Nature Biotech* 30(7).
9. David R., Doherty A. 2017. Viral vectors: the road to reducing genotoxicity. *Tox Sci* 155(2):315–25.
10. Dunbar C, et al. 2018. Gene therapy comes of age. *Science* 359(175).
11. U.S. Food and Drug Administration. Cellular and gene therapy guidances. <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm>
12. Marks P. FDA gene therapy IND applications submitted per year. Data adapted with permission from Peter Marks, Director, FDA Center for Biologics Evaluation and Research (CBER).
13. National Institute of Allergy and Infectious Diseases. Ebola vaccine webpage. <https://www.niaid.nih.gov/diseases-conditions/ebola-vaccines>
14. University of Minnesota Center for Infectious Disease Research and Policy. 2019. Ebola cases climb by 44 as vaccine trial affirms high efficacy. <http://www.cidrap.umn.edu/news-perspective/2019/04/ebola-cases-climb-44-vaccine-trial-affirms-high-efficacy>
15. National Institutes of Health. NIH guidelines. <https://osp.od.nih.gov/biotechnology/nih-guidelines/>
16. Oversight and Review of Clinical Gene Transfer Protocols: Assessing the Role of the Recombinant DNA Advisory Committee. Historical and Policy Timelines for Recombinant DNA Technology. Copyright 2014 by the National Academy of Sciences.

17. Collins FS. Statement on modernizing human gene therapy oversight.  
<https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-modernizing-human-gene-therapy-oversight>
18. Amended Charter, Novel and Exceptional Technology and Research Advisory Committee (Formerly Recombinant DNA Advisory Committee). 2019. [https://osp.od.nih.gov/wp-content/uploads/NExTRAC\\_Charter\\_041219\\_508.pdf](https://osp.od.nih.gov/wp-content/uploads/NExTRAC_Charter_041219_508.pdf)
19. U.S. Food and Drug Administration. Expedited programs for regenerative medicine therapies for serious conditions.  
<https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm585414.pdf>
20. Terry M. Gottlieb at BIO 2018: 40 gene therapy approvals by 2022. *Biospace*.  
<https://www.biospace.com/article/gottlieb-at-bio-2018-40-gene-therapy-approvals-by-2022/>
21. U.S. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., Ph.D., director of the center for biologics evaluation and research on new policies to advance development of safe and effective cell and gene therapies.  
<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629493.htm>

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## CLINICAL RESEARCHER—SEPTEMBER 2019 (Volume 33, Issue 8)

### HOME STUDY

#### *Breaking New Ground in Recruitment and Management for Trials*

##### **Perspectives on Successes and Challenges in the Recruitment and Retention of Pregnant Women in a Research Study**

###### LEARNING OBJECTIVE

After reading this article, the participant will be able to describe the role of, and challenges faced by, research nurses/study coordinators in recruiting and retaining pregnant women in research studies.

###### DISCLOSURE

Amy Rider, RN; Christine Aubry, RN, Sara Moyer, RN; Patricia Kinser, PhD: *Nothing to disclose*

##### **1. How did the study team build relationships to engage in effective recruitment?**

- A. By offering bonuses to staff in their institution for finding study volunteers and using electronic health records.
- B. By creating a new recruitment unit for non-medical intervention studies and using existing vendors.
- C. By capitalizing upon contacts within their institution and using active and passive recruitment methods.
- D. By outsourcing the recruitment to a sister institution and using data from pregnancy support groups.

##### **2. Which of the following is cited as an example of an access point targeted for referrals of potential study participants?**

- A. Local legal aid services
- B. Funeral homes
- C. Child welfare offices
- D. Clinics of psychologists

##### **3. The authors recommend which of the following as a tactic for maintaining professionalism in flyering?**

- A. Asking permission to post when necessary.
- B. Making donations to the owner of the site being used.
- C. Posting only within five miles of the study center.
- D. Restricting the flyer's size to standard postcard dimensions.

**4. Which of the following is an example cited as an “outside the box” entry point for the study’s recruitment?**

- A. Family reunions at local public park
- B. Tent revival meetings in nearby rural district
- C. Doula sessions at local library
- D. Tailgate parties at university sporting events

**5. What do the authors suggest regarding recruitment in low-income housing developments?**

- A. They may be inefficient targets due to extra layers of institutional review board involvement.
- B. They may be rewarding targets for recruiters seeking diversity in their participants.
- C. They may be inefficient targets because nearly all the volunteers can be expected to drop out.
- D. They may be rewarding targets for recruiters seeking to cut the costs of outreach efforts.

**6. Which of the following is mentioned by the authors as an example of a change to the study design affecting flexibility for participants?**

- A. Obtaining approvals to allow participant baseline visits by phone or in person.
- B. Obtaining approvals to allow participants to volunteer for simultaneous studies.
- C. Obtaining approvals to allow participant informed consent to be done electronically.
- D. Obtaining approvals to allow participants to refer friends and family to join the study.

**7. Which of the following was involved in active recruitment for the study regarding waiting room settings?**

- A. Conducting a background legal review of the potential participant’s history with the hospital.
- B. Obtaining blood and urine samples before sharing information about the study.
- C. Conducting a basic medical record review prior to approaching potential participants.
- D. Obtaining proof of insurance before sharing information about the study.

**8. What qualities of their communication with participants are cited by the researchers as being motivational?**

- A. Practical, non-medical
- B. Plain, non-commercial
- C. Private, non-denominational
- D. Personal, non-judgmental

**9. How did the study address participants’ concerns about transportation to the site?**

- A. By arranging for bus transportation.
- B. By arranging for van transportation.
- C. By arranging for Uber/Lyft transportation.
- D. By arranging for subway transportation.



**10. The authors propose which of the following strategies to benefit future studies?**

1. Identify communication “champions” for the study.
2. Convey professionalism and empathy in advertising.
3. Plan a mix of active and passive recruitment.
4. Double the study budget and geographic reach.

- A. 1, 2, and 3 only
- B. 1, 2, and 4 only
- C. 1, 3, and 4 only
- D. 2, 3, and 4 only

### **Established Safety Profiles Allow for a Gene Therapy Boom and Streamlining of Regulatory Oversight**

#### LEARNING OBJECTIVE

After reading this article, the participant should be able to describe the historical growth in, and challenges faced by, gene therapy research and the current state of regulatory focus on the field.

#### DISCLOSURE

Daniel Eisenman, PhD, RBP, SM(NRCM), CBSP: *Nothing to disclose*

**11. The author cites the death of Jesse Gelsinger as an example of what in gene therapy trials?**

- A. Breakthrough therapeutic
- B. Regulatory burden
- C. Improper informed consent
- D. Serious adverse event

**12. Which of the following trends is said to go along with the rise in investigational new drug applications received by FDA for gene therapy products?**

- A. A surge in investigator-initiated trials.
- B. A focus on reassessing safety.
- C. A decline in product approvals.
- D. A lack of sponsor funding.

**13. Gene therapy studies are dominated by activity in which therapeutic area?**

- A. Central nervous system
- B. Respiratory and cardiovascular
- C. Oncology
- D. Allergy

**14. Single gene mutations are addressed in many gene therapy studies despite which of the following factors?**

- A. Their rarity.
- B. Their expense.
- C. Their complexity.
- D. Their controversy.

**15. Why might gene therapy studies require additional review?**

- A. Due to the trials' tendency to fall short on enrollment.
- B. Due to them being considered illegal in many states.
- C. Due to risks associated with engineered genetic materials.
- D. Due to excessive drop-out rates of participants during long studies.

**16. Institutional biosafety committee (IBC) review of gene therapy research applies to sites in which of the following situations?**

- A. The site is under or ever has been under investigation by FDA.
- B. The site receives or ever has received NIH funding for research.
- C. The site handles or ever has handled radioactive investigational products.
- D. The site participates or ever has participated in multinational trials.

**17. Those conducting multisite trials may benefit from which of the following review tactics?**

- A. Using locally administered data safety reviews.
- B. Using nationally administered budget reviews.
- C. Using centrally administered IBC reviews.
- D. Using anonymously administered participant reviews.

**18. Revisions to NIH Guidelines in 2019 removed which of the following requirements for gene therapy studies?**

- A. For IRB and IBC judgement regarding FDA Center for Biologics Evaluation and Research review.
- B. For IRB and IBC determination regarding HHS Office for Human Research Protections review.
- C. For IRB and IBC judgement regarding CMS national coverage determinations.
- D. For IRB and IBC determination regarding NIH Recombinant DNA Advisory Committee review.

**19. Which of the following is cited as now being a responsibility under an amended charter for the advisory committee known as NExTRAC?**

- A. Advising the NIH Director regarding emerging technologies in biomedical science.
- B. Advising the NIH Director regarding issues of fraud and waste in biomedical science.
- C. Advising the NIH Director regarding reports of adverse events in biomedical science.
- D. Advising the NIH Director regarding retractions of published research in biomedical science.

**20. The author cites which of the following as steps taken by FDA to advance gene therapy development?**

1. Issuing of guidances
  2. Designation of RMAT
  3. Dedication of funding
  4. Expansion of reviews
- 
- A. 1, 2, and 3 only
  - B. 1, 2, and 4 only
  - C. 1, 3, and 4 only
  - D. 2, 3, and 4 only