RESEARCH PRACTITIONER

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25 Years

Lessons learned from oncology research: Put patients at the center and embrace new tools and strategies

by Elizabeth Tilley Hinkle

Oncology trials often lead the research innovation pack, from deploying diverse data sources to using novel recruitment methods to embracing new trial designs. While some advances are specific to cancer research, research-ers in all fields can look to oncology studies to improve their own trials, especially when it comes to patient centricity and harnessing the power of new tools and strategies.

Biomarkers and other precision medicine techniques, for example, provide a more customized and personally meaningful research experience to participants. Adaptive trial designs and new technologies can produce more meaningful data. And oncology research teams have made great strides in incorporating patient perspectives and preferences into their studies by giving weight to patient-reported outcomes, quality-of-life measures and shared decisionmaking.

Patient-centricity focuses on trust, engagement

Although patients are key participants in clinical research, they have had a limited role in the design and decision-making process, with clinical experts and healthcare providers taking the lead, Eliya Farah and his colleagues from the Life-Saving Therapies Network and the University of Ottawa note in *Current Oncology*.[1] But patients can play an instrumental role in clinical trials,

Learner Outcomes:

1. Explain why oncology research is a leader in patient centricity.
2. Describe the advanced tools and methods oncology studies employ.
3. List areas of research that are well-suited to emulate oncology study methods.
4. Discuss the overall state of the research field and potential advances in the future.

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National Academies report urges greater inclusion of pregnant participants in clinical research

by Elizabeth Tilley Hinkle

Clinical trial professionals and academic organizations have long been cautious about the safety and legal liability of including pregnant or lactating participants in studies. But a recent report from the National Academies of Sciences, Engineering and Medicine (NASEM) finds limited evidence to support those fears.[1] The report also warns that the lack of evidence available to these patients and their doctors about using a drug or vaccine poses greater potential harm than including them in research would.

As for safety, the report, ordered by Congress, shows that there have been no reported adverse effects specific to pregnant clinical trial participants since 1962, when the FDA was granted authority to require proof of safety and efficacy of products before they go to market. The report does note that one marketed drug was the subject of several

Learner Outcomes:

1. Explain the historic perceptions about including pregnant people in research.
2. Discuss the benefits of including pregnant people in clinical trials.
3. List precautions researchers can take to protect pregnant and lactating populations.
4. Describe tools and strategies to ensure safe and equitable participation in trials.

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Continuing Education Credit Program

Research Practitioner readers can earn 3.0 continuing education credits per issue. When accepted by self-report on ACRPnet.org, credits can be used to maintain certification in ACRP's Certified Clinical Research Coordinator (CCRC®), Certified Clinical Research Associate (CCRA®), Certified Principal Investigator (CPI®) and Certified Professional (ACRP-CP®) programs. The course is also eligible for those persons self-reporting maintenance of certification credits to retain SOCRA CCRP® certification designation.

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Overview: *Research Practitioner* is a bimonthly journal designed for clinical trial professionals seeking to advance their knowledge of the trials industry, improve job skills and pursue professional certification. Articles focus on the methods and practice of clinical trials, including deep dives into industry trends, introduction to new concepts and insight into experts' thoughts on issues of importance to the industry.

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Overall Learner Outcomes: After reading an issue of *Research Practitioner*, clinical trial professionals should be better able to:

- Discuss current thinking regarding specific methodologies in the design and execution of clinical trials;
- Apply ethical and legal principles for the conduct of research and the protection of human research subjects; and
- Conduct clinical trials to comply with U.S. and global regulations.

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Regulatory Update

Contact hours not offered for these articles

FDA Guidance Outlines Procedures for Handling, Retaining BA, BE Test Samples

The FDA's guidance on the quantity of bioavailability (BA) and bioequivalence (BE) testing samples to be retained by NDA applicants and contract research organizations (CRO) contains both draft and final language focusing on both the test article and reference standard.

The 22-page guidance's final section, which covers quantity of reserve samples, is implemented immediately. The agency said it is activating this section of the guidance without prior public comment, deeming that prior input is not necessary as the guidance offers a less burdensome policy consistent with public health.

Revising the agency's now withdrawn August 2020 Compliance Policy on the subject and superseding its 2004 guidance, the guidance also describes conditions under which the FDA does not generally take enforcement action against an applicant or CRO for retaining less than the quantity of reserve samples of the drug (test articles and reference standards) used in an in vivo BA or in vitro BE study.

The draft guidance offers drugmakers, site management organizations and CROs recommendations on procedures for handling reserve samples from relevant BA and BE studies.

Comments on the draft portion of the guidance are due by June 27.

View the guidance here.

EMA Launches Collaborative Trial Enhancement Effort

As part of its Accelerating Clinical Trials in the EU (ACT EU) initiative, the European Medicines Agency (EMA) has established a collaborative, multistakeholder platform to facilitate discussion on comprehensively improving clinical trials in the EU.

The platform, led by an advisory group of key stakeholder representatives, will host regular meetings at which stakeholders from across the clinical research spectrum can discuss and share perspectives on key topics, including trial design and conduct, statistical analysis, regulatory optimization, data transparency and patient engagement, with specific topic groups supporting technical discussions. Consultations, surveys and other tools will also be used to obtain feedback.

Access the platform's anticipated schedule here.

New CDER Hub Seeks Innovative Trial Designs for Demo Project

A new CDER subcenter is looking for drug developers with specific in-process studies for a demonstration program intended to boost innovation in clinical trial design.

The Center for Clinical Trial Innovation (C3TI), activated on April 15, will choose up to nine sponsors with innovative clinical trials currently under a pre-Investigational New Drug (IND) or IND designation with CDER. The trials must be intended to support new drug approvals or changes to approved drug labeling.

Applicants for the C3TI Demonstration Program should be conducting either point-of-care or pragmatic trials, Bayesian analyses or trials using selective safety data collection. Sponsors chosen to participate will be expected to share details of their trials and the implementation of trial innovations as they progress, CDER said.

As the work of C3TI grows, it will serve as a central hub that will disseminate lessons learned

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from the demonstration program across CDER's existing trial innovation programs.

Additionally, the center aims to help stakeholders involved in clinical research stay current with trial innovations; improve the efficiency and effectiveness of trials; increase the participation of diverse populations; enhance the quality of trial data; and accelerate the development of safe and effective new drugs.

Read more about the C3TI Demonstration Program here.

FDA Kicks Off Next Gen Home Healthcare Device Development Program

The FDA's Center for Device and Radiological Health (CDRH) has launched a new initiative to deliver virtual reality-enabled models for use in the development of home-based care solutions and expansion of decentralized trials.

The Home as a Health Care Hub program, a collaboration between the agency, patient groups, providers and other device industry stakeholders, will see the design of augmented reality/virtual reality (AR/VR) home models that can be used as sandboxes for designing and evaluating at-home healthcare solutions.

The initial prototype will focus on rural and lower-income dwellings with a goal of advancing health equity and is expected later this year.

This "prototype is the beginning of the conversation — supporting device developers' novel design approaches, helping providers consider opportunities to educate patients and extend care options, generating discussions on value-based care paradigms, and opening opportunities to bring clinical trials and other evidence generation processes to underrepresented communities through the home," CDRH Director Jeff Shuren said.

EU Offers Direction on Developing Investigator Brochures for Device Trials

The European Commission's Medical Device Coordination Group (MDCG) has issued guidance advising sponsors to include both clinical and preclinical information in the investigator's brochure when applying for medical device trial authorization.

The 34-page guidance instructs applicants to provide a brochure "in a concise, simple, objective, balanced, and nonpromotional form that enables a potential investigator and the investigation site team to understand it and make his/her own unbiased benefit-risk analysis of the appropriateness of exposing study participants to the investigational device."

In addition, MDCG expects sponsors to alert investigators to any updates to the brochure or newly available information in a timely manner. Any member states involved in the trial must also be informed of any changes to the IB within one week, the guidance notes.

Read the full guidance here.

FDA, NIH Seek Input on Clinical Trial Innovation Glossary

The FDA and NIH are asking stakeholders for support in developing a glossary of terms related to clinical trial innovation, especially terms involving use of real-world data (RWD) and real-world evidence (RWE).

Through a working group formed to develop definitions, the FDA and NIH aim to target industry's inconsistent use and understanding of certain terms, especially descriptions of innovative trial designs and certain trials that use RWD to generate RWE, the agencies said in their announcement. The goal is greater clinical research efficiency and communication.

Specifically, the FDA and NIH would like to know:

- If the glossary's terms support a shared understanding of terms for describing clinical research
- If there are potential improvements to be made to the terms or potential hurdles to their widespread use or implementation
- If any terms should be removed, including the reasons for removal
- If there are other terms that see inconsistent use across the research enterprise

"In some cases, this lack of a consistent terminology results in diminished clarity where the same term may have different meanings to different parties. In other cases, inconsistent usage of terms has created specific challenges to understanding the intended meaning and impact of terms (e.g., pragmatic clinical trial, pragmatic elements, causal inference)," they said. "These challenges may be particularly apparent when describing a study design in a protocol, communicating about planned research studies, or interpreting and describing research results.

Stakeholders may submit comments until June 24.

Read the draft glossary here.

Read the request for information here.

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starting from the initial design, they add.

"The future of clinical trials should prioritize patients' values and perspectives, with regulatory bodies fostering these practices through clear guidelines, Farah et al. write. "As the concept of patient centricity takes root in oncology research, the involvement of patients should evolve beyond mere participation."

"Their unique insights and experiences could guide the formation of research questions and shape a study's framework," the authors add. "Their input becomes crucial during pretrial preparations, with feedback on measures, treatments and interventions contributing to a protocol that is reflective of and responsive to the needs and preferences of participants."

Patient-centric trials lead to higher levels of patient engagement, which in turn drives better data collection and retention rates, according to life sciences consultancy Proventa.[2]

Trust and transparency are central to patient-centric research, writes Jon Morris, vice president and CMO of CRO IQVIA.[3] Involving patients more closely in every phase of the research process to ensure that research objectives align with patient needs and expectations can play a major role in building both, he writes.

Participant input paired with clear communication about the research process, goals and outcomes can help demystify the research process, leading to higher patient engagement and retention as well as more open patient feedback, which provides valuable insights that might otherwise be overlooked. And this makes the data quality richer, while expanding insights that might be missed if the focus is only on quantitative data, such as clinical outcomes and biomarkers.

Data quality can also improve in this environment, according to Proventa: When patients are involved in trial design and monitoring, research teams can gather more comprehensive and accurate data, which helps the credibility and reliability of study results.

One reason oncology research is leading the field in this area is that oncology trials often involve different efficacy endpoints. Rather than focusing only on how effectively a drug treats a disease or condition, many oncology clinical trials aim to extend or improve patients' quality of life, notes CRO Simbec-Orion.[4] Some, for example, may aim to reduce the impact of treatment side effects or ensure that patient quality-of-life priorities are addressed.

And most areas of research could benefit from the trust-building aspect of patient-centered clinical trials.

Technology aids diverse data collection, interpretation

Incorporating patient-reported outcomes and using remote technology to increase participant convenience means that research teams must integrate more diverse types of data, such as from wearables, mobile health apps and electronic health records (EHR) Morris notes.

These sources offer continuous real-time data that can provide deeper insights into patient behaviors and experiences. But these tools require meticulous attention to data quality to ensure accuracy, completeness and consistency, Morris emphasizes. In patient-centered research, this means capturing clinical measurements accurately and ensuring systematic and thoughtful collection of patient-reported data.

This data can be used to provide invaluable insights into patient behaviors, treatment responses and health outcomes, he adds. The result should be more dynamic and responsive research models. Technology and innovation will be pivotal in making this shift. Artificial intelligence and other advanced data analytics tools will be crucial to manage and interpret all the varied data. Technology reveals patterns that would otherwise be impossible to detect.

Digital platforms facilitating direct patient engagement and communication will become increasingly important, allowing continuous interaction between research teams and patients as well. "The emphasis should be on creating robust data management systems that can handle diverse data types for data utilization," Morris writes. "Employing data standardization protocols and ensuring data interoperability is key to efficient data utilization. Researchers should also focus on developing patient-centered outcome measures that accurately reflect patient experiences and priorities."

Another challenge can lie in engaging a diverse patient population. Such factors as awareness of clinical trials, mistrust in research and logistical barriers can loom large, Morris says. To address these, research teams must use more inclusive recruitment strategies that employ community engagement tactics and the support of patient advocates, for example. Simplified consenting processes can also enhance patient participation.

Outreach key to patient-centric approach

Improved means of getting patients into appropriate clinical trials can be the first step toward a patient-centric approach. Patient enrollment in clinical trials requires that their doctors be familiar with both open protocols and the fine details of eligibility requirements, Memorial Sloan Kettering Cancer

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Center's Bob Li and researchers from several other academic medical schools and providers note in *Nature Medicine*.[5] And this can be challenging due to the growing complexity of trials, including a greater number of screening procedures and strict eligibility criteria, which are often biomarker-specific.

Oncology research has a unique pipeline, in that doctors and patients discuss available clinical trials after a cancer diagnosis more often than they do with other diagnoses. But oncology still has lessons to share with other fields when it comes to access, Joseph Unger and his colleagues at the Fred Hutchinson Cancer Research Center note in volume 36 of the American Society of Clinical Oncology's Educational Book series.[6]

A key barrier is lack of integration between patient care and clinical research, particularly in underserved communities, they write. Additional challenges come from inequitable access to biomarker testing and next-generation sequencing.

Overly restrictive inclusion/exclusion criteria can further limit trial participation, Li et al. say. In addition, when the inclusion criteria are very narrow, the generalizability of trial data to real-world populations may be compromised, they add.

Oncology researchers were among the first to evaluate the barriers that patients may face to clinical trial participation. Unger et al. break these barriers into categories:

- Structural, such as absence of an available clinical trial or lack of access to a cancer clinic
- Clinical, such as when a patient does not meet eligibility requirements, especially with protocols that include very narrow inclusion criteria
- Attitudinal, with respect to both patients and physicians
- Demographic and socioeconomic

There is a lot of overlap among these categories. For example, socioeconomic status can affect such key factors as transportation, ability to afford travel costs and access to insurance and to childcare. Similarly, different socioeconomic statuses can be associated with different demographics, including race, age and gender.

A key feature of patient-centric research includes reforming the consent process with patient input. This helps ensure that consenting involves clear, understandable information to patients, Proventa notes.

Patient-centric research is a trend likely to continue and could lead to an upsurge in personalized medicine, including on the research side, Morris writes, driven by better understanding of individual patient needs.

"This shift will be characterized by a move towards more tailored treatment strategies instead of the one-size-fits-all approach that has dominated traditional research. The focus will be on how individual genetic, environmental and lifestyle factors influence health, leading to more effective and targeted therapies," he says.

Biomarkers refine research targets

Oncology research has taken a lead in using biomarkers to improve diagnostic accuracy and treatment selection: identifying and validating biomarkers to predict treatment response, disease progression and patient outcomes based on specific genetic characteristics that can vary from patient to patient.

A biomarker is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions," Stephane Chauvie and colleagues from a variety of academic medical schools in the US and abroad write in *Tomography*.[7] Biomarkers are used to diagnose and stage cancer, target surgery or radiotherapy treatments, guide patient stratification for clinical trials and predict and/or monitor therapeutic efficacy. They can also be used as predictors of traditional endpoints, such as treatment response and survival.

While the bulk of biomarker use to date has been seen in the oncology arena, the tools also show promise in other areas of research, Ali Bodaghi of Iran's Islamic Azad University and coauthors from other research organizations note in *Heliyon Journal*.[8] A variety of diagnostic biomarkers show promise. Imaging biomarkers, for example, can be used not only to diagnose and stage cancer but also to better understand neurodegenerative diseases. Examples include cardiac troponin to diagnose cardiac muscle injury, glutamate for altered metabolism and cystatin-C for estimating the severity of renal injury or oxidative stress.

Some special considerations apply to biomarkers in clinical trials. For example, trial designs and analysis plans require additional considerations that depend on the nature of the biomarkers, such as whether they are prognostic vs. predictive or integral vs. integrated, John Hopkins University's Chen Hu and James Dignam write in *Precision Oncology*.[9] They also depend on the credentials of biomarkers' performance and clinical utility. (A biomarker with strong credentials is one that

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has convincing evidence that the benefits of a treatment are limited to a biomarker-positive subgroup.)

The concept hinges on integrating the right biomarker information to properly select trial cohorts for patients most likely to benefit from a particular therapy.

And the consequences of asking the right or wrong questions in biomarker-driven clinical trials can be serious, Chen and Dignam note. For example, a good biologic rationale may exist to consider biomarker negative patients less likely to benefit from a new targeted therapy. But the clinical evidence of whether that treatment will only benefit biomarker positive patients may or may not be strong.

Additionally, development of a validated companion biomarker may lag behind development of novel therapies.

"Therefore, as we simultaneously evaluate new treatments and identify new patient populations defined by the corresponding biomarkers, it is crucial to properly tailor the trial designs and prioritize research questions on the basis of the development stage of the biomarker and the credentials of its clinical utility," Hu and Dignam write.

Special contractual considerations also may apply when biomarkers are used in clinical trials, CRO Precision for Medicine notes in a post.[10] Sponsors and CROs must have agreements with sites that allow for access to specific subject and biomarker data. Close collaboration among trial partners could also enable sharing of blinded biomarker data to inform site selection in future clinical studies.

Biomarkers have applications beyond oncology research

A related area is precision medicine, in which treatment can be tailored based on specific disease characteristics in a given patient. Precision medicine has the potential to allow more personalized approaches for other conditions, as well, with consideration given to varied treatment responses among patients with different characteristics.

This approach springs from the recognition that individuals with the same disease are complex and differ from each other. Traditionally, heterogeneity across clinical trials has been underestimated, researchers at Shanghai's Changzheng Hospital, including Xiao-Peng Duan, write in *Signal Transduction and Targeted Therapy*.[11] Researchers developed patient-centric trials aiming to provide optimal therapy customization to individuals with specific biomarkers. These include the basket, umbrella and platform trial.

Precision medicine focuses on selecting reliable biomarkers that predict how effectively a therapy will work for a specific group of patients, Edoardo Crimini and colleagues at Italy's European Institute of Oncology and other academic organization note in *Cancer Treatment Reviews*.[12] This is different from personalized medicine — although the two terms often are used synonymously — which refers to the rationalization of therapeutic choices for each individual patient, they note.

And oncology research has been at the forefront of this approach to develop more effective cancer treatments and reduce chemotherapy side effects. This is closely related to biomarker-guided research, Duan et al. note.

For example, the National Cancer Institute Molecular Analysis for Therapy Choice trial showed that people with advanced cancer may benefit from genomic sequencing to help plan their treatment.[13]

This approach could be applied to other diseases as well. In fact, precision medicine could be relevant for any disease with multiple potential causes that result in similar collections of symptoms, according to AstraZeneca.[14] Precisely targeting molecules that stimulate inflammation in the lungs in patients with respiratory diseases such as asthma or chronic obstructive pulmonary disease, for example, could lead to novel precision medicines. Chronic kidney disease could also be a target for precision medicine clinical trials in the near future, according to AstraZeneca.

Adaptive trial designs support precision medicine

Challenges come in designing trials to effectively study precision medicine techniques. Current understanding of these new trial designs, compared to traditional trials, is still limited, Duan et al. write. "The majority of the research focuses on methodologies, and there is a lack of in-depth insight concerning the underlying biological logic of these new clinical trial designs."

For this reason, there is a close link between precision medicine, use of biomarkers and adaptive trial designs. Adaptive designs allow sponsors and research teams to adjust key parameters, such as dosages or endpoints, in response to evidence that arises as they collect and analyze data.

The notion of adaptive research strategies is closely linked to biomarkers. Hu and Dignam note that adaptive strategies (trial modification based on accumulated information) was already a common feature in oncology trials before biomarkers were a design focus.

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Designs like basket and umbrella trials can meet that need and the number of such studies has rapidly increased, Duan et al. report. Both trial designs use a molecular screening protocol that either permits the enrollment of different diseases with a certain characteristic or disease with different subtypes. Both designs use a fixed protocol at a specific time, however, which limits the efficiency of trials with the rapid development of precision medicine.

A new design that would be adaptable and responsive to emerging evidence would be an ideal solution, hence the rise of the platform or multi-arm, multistage trial. This design continuously assesses several interventions against a certain disease and adapts the trial design based on the accumulated data. This allows for early termination of ineffective interventions and flexibility in adding new interventions during the trial.

The basket design has been guided by the pan-cancer proliferation-driven molecular phenotype in oncology research. This design was developed with the idea of treating the same disease with different treatments based on different molecular phenotypes of a given disease. In other words, it evaluates multiple interventions within a particular disease in a single trial.

For example, lung cancer was initially treated as a single disease with varying outcomes. Later, outcomes were significantly improved by using different treatment approaches when lung cancers were categorized into subtypes that include adenocarcinoma, squamous cell carcinoma and small cell lung cancer. And with precision medicine, various mutations associated with each have been observed, resulting in greater efficacy by administering targeted therapies based on specific gene mutations.

Therapies based on similar molecular alterations distributed in different anatomical cancer types accelerate development of cancer treatments. HER2 in breast and bladder cancers, associated with chemotherapy resistance, is an example.

This concept can also be applied in other clinical fields, such as Alzheimer's disease, vasculitides, metabolic diseases and infectious diseases, Duan et al. write.

Both basket and umbrella trials rely on drugs or interventions limited to a certain time point, which precludes dynamic adaptation to emerging evidence. A dynamic perspective, however, is important to precision medicine, particularly in consideration of disease evolution and the rapid emergence of novel drugs and interventions.

A platform trial offers a flexible and adaptive design allowing for simultaneous evaluation of multiple interventions or treatment strategies against a single control arm for a specific disease within a unified framework. Interventions that show promise can be added while those with insufficient evidence of activity over time can be removed within the prespecified protocol.

The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial was the first multi-arm platform trial in high-risk localized or metastatic prostate cancer, Duan et al. note. A notable feature of STAMPEDE was its adaptive design. Only six arms were included when the trial was initiated in 2005. Eleven interventions had been added by the time it closed in 2023.

Collaborative networks are burgeoning trend

One of the features of platform trials and other adaptive designs is promotion of collaboration and data-sharing among research teams and clinicians. There has been a recent push in the clinical research arena for greater sharing of data among different research institutions. In the study of oncology and rare diseases, in particular, collaborative research networks that share data on developing treatments can boost the pace of research efforts and aid in identifying and recruiting appropriate patients for novel treatments.

Oncology research often involves networks of clinicians and research institutions, particularly for identifying patients that meet criteria for trial enrollment, which often is highly specific.

Over the past decade, pharma companies have established collaborations with universities and public research centers following the model of open innovation. The collaborations are carried out via networks that include actors with distinct characteristics for purposes of resource exchanges in technological development, Giovana Fiori and coauthors, all affiliated with Brazil's Ribeirão Preto University of São Paulo, write in *Technological Forecasting and Social Change*.[15]

For example, investigators at Moffitt Comprehensive Cancer Center and a group of US collaborators designed the Oncology Research Information Exchange Network (ORIEN) to provide greater access to clinical trials specific to an individual's genomic cancer type. This initiative gathers clinical data and tumor and germline DNA for prospective tumor typing, West Virginia University's Richard Goldberg and coauthors from Ohio State University explain in *Oncologist*.[16]

This allows genetic analyses to be done early so patients can be matched to studies specifically targeting their cancers'

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precise mutations. Enrolled patients then also contribute to the data bank used to design new trials.

Data-sharing plans through networks such as ORIEN "will provide more reliable and extensive historical data, which will lead to better study designs and thresholds determination," Goldberg et al. write.

The COVID-19 pandemic also offers an example of how research and innovation supported recovery from the global health and economic impact, according to Chibuzor Uchea, senior research manager at Wellcome Trust. Similarly, efficient development of solutions for drug-resistant infections is a key solution to antimicrobial resistance.

When researchers, product developers, industry, funders, philanthropists and governments worked together to develop COVID-19 treatments, diagnostics and vaccines, it marked an important shift in how studies can be conducted.

"Collaborative research networks reflect the values and priorities of their members," the University of Toronto's Karen Burns and her coauthors from other Canadian research organizations write in the *American Journal of Respiratory and Critical Care Medicine*.[18] "In turn, they are responsive to members' needs and transcend the focus on specific investigations to address broader issues, including research methodology and implementation. Collaborative research networks are better equipped than local investigative teams to address research questions and bring large studies to completion."

Fiori et al. report that associations of clinical trial networks tend to have more partnerships than patient networks, which indicates greater trust and the need for complementary expertise. During R&D stages of new oncology drugs, organizations search for actors of different types, as experts are required for each stage.

Uchea notes that Wellcome advocates for more cohesive ways of working in the field of antimicrobial resistance research. Clinical trial networks — collaborative structures designed to support and enhance the efficiency and quality of clinical research through harmonization, cooperation and resource-sharing — can foster international collaboration and speed treatment development.

Immunotherapy shows promise in trials outside oncology

Finally, immunotherapy is an area that has shown promise for certain types of disease. Over recent years, oncology research has made strides in this area. Examples include investigating anti-PD-(L)1 agents for intrathoracic tumors.

Immunotherapy can take several different forms, according to the Moffitt Cancer Center. These include adoptive cell transfer, techniques that include CAR-T technology to modify T-cells with cancer-fighting antigen receptors, along with:

- Cytokine therapy
- Immune checkpoint inhibitors
- Monoclonal antibody immunotherapy
- Vaccines

These techniques have been successfully studied as treatments for a variety of cancers, including breast cancer, cervical cancer, lung cancer, lymphoma, melanoma and more, Moffitt reports.

Although primarily used in cancer treatments, immunotherapy can also be used to treat autoimmune diseases and disorders, according to a report from the University of Chicago.[19] These include genetic disorders, inflammation, diabetes, cardiovascular diseases and regenerative medicine.

Immunotherapy agents have shown unprecedented response rates and long-term benefits in various settings, Everardo Saad and his colleagues at Belgium's International Drug Development Institute agree in *Cancers (Basel)*. These advances have pointed to the need for new or adapted approaches to trial design and efficacy and safety assessment.[20]

Whether it's patient-driven endpoints and outcomes, technology to gather different types of data or application of biomarkers and precision medicine techniques, novel approaches to clinical research are almost certainly here to stay. While few of these features could be considered universally applicable, there are a variety of lessons learned under the oncology arena that could benefit many other areas of clinical research.

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reported cases involving injury to lactating patients but no injury to their children.

Considering liability, there are claims of harm for pregnant people who take approved drugs and products but little evidence of harm directly stemming from enrolling pregnant or lactating participants in clinical trials. Which raises the question: Could that liability have been avoided if pregnant patients had been included in clinical research for those products in the first place? Evidence suggests the answer is "yes," according to the report.

The report calls for a change to the status quo and urges new, clearer guidance from the FDA on enrolling pregnant and lactating participants in clinical trials. Further, the report urges the agency to use the theoretical new guidance to specifically recommend including pregnant and lactating participants in trials unless available clinical and preclinical safety and efficacy data raise any red flags, in order to address that third concern: ethics.

Rather than trying to "protect" pregnant and lactating patients, the FDA should require that diversity action plans include them.

Sponsors would be responsible for raising any concerns and submitting justification to the agency for excluding members of these populations.

The guidance should also include suggested study designs, safeguards and product-specific monitoring, all of which NASEM says will help investigators and sponsors safely conduct trials that include pregnant or lactating participants. Other recommendations in the NASEM report include:

- HHS should form an interagency task force, which would include FDA, NIH, the CDC and other agencies to maintain infrastructure and guidelines for pregnancy and lactation safety studies for approved products.
- HHS' Office for Human Research Protections should provide clear guidance on protections for pregnant or lactating clinical trial participants.
- NIH should develop a plan to prioritize research that includes pregnant and lactating participants.
- Congress should pass legislation to incentivize studies to include information about labeling products for pregnant and lactating patients, modeled after legislation to address evidence gaps for therapies intended for children.
- Congress should also authorize the FDA to require research related to the use of drugs, biologics, medical devices and vaccines in pregnant and lactating patients.

All these recommendations, if taken up at all, will take time to come to fruition. But even under existing regulations and guidance documents, there are steps sponsors and researchers can take to get ahead of the likely shift to including pregnant participants in more clinical trials.

An overly protectionist ethic

Underrepresentation of pregnant people is often attributed to safety concerns, associated liability, regulatory responses and the preferences of the pharma industry, Tara Coffin and Sharad Adekar, WCG institutional review board (IRB) chair/vice chair and medical chair, respectively, write in *Clinical Researcher*.[2] This can be the case even when there is possible benefit to the pregnant person and fetus or newborn. In essence, pregnant participants are treated as a vulnerable population.

Traditionally, a protectionist ethic has been applied to clinical research in pregnant people, the FDA's Catherine Sewel, along with agency colleagues and academic coauthors, notes in the *American Journal of Obstetrics & Gynecology*.[3] This ethic can be seen, for example, in a regulation that requires both paternal and maternal consent when a potential benefit of an investigational product applies only to the fetus.

And there's cause to be cautious about exposing a fetus to drugs, since some are known to be harmful to an unborn child, the University of Liverpool's Catriona Waitt and her government and academic coauthors note in *Communications Medicine*.[4] But there is a misconception that not testing new products in pregnant individuals reduces the risk to zero. If a drug, after approval, is prescribed to pregnant people or those with childbearing potential, fetal exposure will occur. And outside a clinical trial context, these exposures will not be carefully monitored and there could be a delay in recognizing any adverse effects. This concept is referred to as risk-shifting.

As part of this ethic, participation in some clinical trials requires contraception, for example, even if it would not be otherwise needed. Requiring contraception for participants with no prospect of pregnancy — such as a patient in a same-sex relationship — raises ethical concerns by imposing unnecessary requirements that could prevent participation in a study, Sewell et al. note.

But this limits the autonomy of pregnant patients, excludes them from research and exposes them and their children to

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harm due to constrained evidence, they add. It also fails to consider the role altruism may play in patients opting to participate in clinical trials when the research could benefit other pregnant people.

And the reality is that failure to include pregnant participants in trials of new products could actually increase a sponsor's liability, Sewell et al. write. While premarket testing is not risk-free, the liability is limited to the size of the research population and largely mitigated by full informed consent. However, legal risk increases substantially after a drug enters the market if adverse events occur in a patient population that was excluded from clinical research, they note.

Perceptions of liability are a key driver of the traditional reluctance to include pregnant participants in clinical trials routinely. But it isn't the only factor. Sewell et al. point to three other key considerations that influence sponsor decisions to exclude pregnant trial participants as well as those who may be breastfeeding:

- The mistaken notion that including pregnant patients is forbidden by law and/or regulations. In fact, FDA guidance and federal regulations provide criteria for including pregnant people in clinical trials.
- Current federal regulations are ambiguous, neither requiring inclusion of pregnant participants in research nor penalizing exclusion of these patients. Additionally, key terms in the regulations, such as "minimal risk," can be open to a variety of interpretations.
- Increased trial and overhead expenses, such as additional liability coverage, associated with inclusion of pregnant people in a clinical trial. Inclusion may also slow trial recruitment if a minimum sample of pregnant people is required. In contrast, exclusion allows researchers to avoid those costs and delays as well as mitigating premarket liability risks in favor of shifting postmarket liability to prescribers and patients.

Significant population data gaps

Ultimately, exclusion of these populations from clinical trials has resulted in a dearth of data about the appropriate dose, efficacy and safety of most medical interventions for pregnant and lactating patients, which could result in greater liability and less effective healthcare. These patients and their doctors must make decisions regarding treatments and vaccines without benefit of high-quality evidence of a product's effects on the patient, fetus or baby, the NASEM report says.

"Significant data gaps around the use of medicinal products during pregnancy and breastfeeding have impeded healthcare decision-making," writes Laura Shaughnessy, clinical program director at biopharma company UCB.[5]

"This lack of information is particularly challenging for individuals living with chronic diseases during the stages of pregnancy and breastfeeding as it does not allow for an informed dialogue with their healthcare providers about optimal management and treatment of their diseases at those times," Shaughnessy, a member of the International Conference on Harmonisation'S E21 expert working group, formed to create guidelines for including pregnant and breastfeeding participants in clinical research. she adds.

Sewell et al. also note that drugs approved for a given medical condition in adults are also approved for use in pregnant adults with that condition unless specifically contraindicated during pregnancy, despite the limited pregnancy-specific data on their risks and benefits in pregnant people.

This is problematic because of the numbers of pregnant and lactating patients that must take medications for pre-existing conditions. According to the NASEM report, for example, about 70 percent of pregnant patients take one or more prescription medications, as do at least half of all lactating patients.

Patients also may seek treatment for conditions unique to pregnancy, such as gestational diabetes, preeclampsia and severe nausea or vomiting, the report adds, even though drugs to treat these conditions were not tested in pregnant clinical trial participants.

The result is treatment of many conditions during pregnancy or lactation relies on drugs that have only observational data to confirm safety, putting the burden on patients and their physicians to decide if the treatment is safe to continue during pregnancy, Harriette Van Spall, an associate professor of medicine at McMaster University in Canada, tells *Clinical Trials Arena*.[6]

These decisions must currently be based on real-world data, case reports and any available information about outcomes among patients who have taken the drug in question, Tracy Caroline Bank, maternal fetal medicine fellow at Ohio State University, told *Clinical Trials Arena*. For example, a patient with Crohn's disease might have trouble finding information about continuing a biologic therapy during pregnancy. There is no data to suggest the drug is dangerous and it is probably better to keep administering it than to discontinue it, she says. But the lack of empirical clinical evidence is a challenge.

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"For example, a pregnant person seeking treatment for gestational diabetes is often limited to 'off label' treatment options — medications or medical devices that have not been formally tested in a prospective interventional study with pregnant participants," Coffin and Adekar write. "Without adequate research data, such treatments are often not approved for use in this population. That doesn't mean they are inherently unsafe, it just means that the safety profile is unclear for pregnant individuals."

The thalidomide tragedy, widely considered the catalyst for the hyper-protectionist attitude toward inclusion of pregnant research participants, can stand as a cautionary tale, according to Miranda Waggoner, associate professor of sociology at Florida State University. The drug, which in the late 1950s was marketed as a treatment for morning sickness but caused severe birth defects in thousands of babies, was not responsibly studied during pregnancy before being prescribed to pregnant patients, she told *Clinical Trials Arena*.

This event could have become a catalyst for expanding and improving responsible studies of drugs in pregnancy, she says. Instead, it had the opposite effect, chilling research in pregnant patients.

A more recent example of pregnancy exclusion can be found in clinical trials of COVID-19 vaccines. As with many other infections, COVID can cause worse outcomes in pregnant individuals. However, pregnant patients were excluded from vaccine trials, Sewell et al. say.

Common Rule confusion

Current regulations and federal guidance covering clinical research specifically address enrollment of pregnant and lactating participants, with a focus on risk mitigation and patient safety. However, no regulations ban inclusion of these groups from research, although certain cautions are emphasized.

However, the wording in regulations and other communications can be confusing. For example, the FDA states on its website: "In general, pregnant [participants] are excluded from drug development clinical trials. However, in certain situations, it may be scientifically and ethically appropriate to include pregnant [participants] in a clinical trial."[7]

A closer read of applicable regulations, however, indicates that the general exclusion of pregnant trial participants may have more to do with unfounded concerns vs. what those regulations actually say.

For any clinical trial supported or conducted by HHS, 45 CFR Part 46 applies.[8] This regulation, often referred to as the Common Rule because it covers research funded by several federal agencies (but not the FDA), requires that all the following conditions be met before a pregnant participant may be enrolled in a clinical trial:

- Preclinical and clinical studies exist that provide data for assessing risks to the pregnant woman and fetus.
- Risks to the fetus may be caused only by therapies with potential direct benefit to the pregnant woman or the fetus. If no such benefit exists, only "minimal" risk to the fetus is permitted.
- Any risk must be the least possible for achieving research objectives.
- If the above conditions are met, the pregnant participant must provide informed consent consistent with regulatory requirements.
- If the potential benefit of the research is solely for the fetus, the consent of both the pregnant participant and the other parent must be obtained in most cases.
- All informed consent procedures and regulatory requirements must be followed.

FDA regulations on ethical conduct of clinical research do not specifically address the issue, but the agency recommends in a 2018 draft guidance on inclusion of pregnant participants in research "that these requirements be satisfied for FDA-regulated clinical research."[9]

That guidance clearly states that the FDA permits inclusion of pregnant people when known risks are not research-related, as described in the Common Rule. For example, a study to assess the pharmacokinetics (PK) of an antidepressant during pregnancy might enroll pregnant people already using the drug in question. In this situation, the drug does not create research-related risks because the enrolled participants were taking it before joining the study. The only risks posed by the study are those associated with specific procedures, such as blood sample collection, and the potential loss of privacy and confidentiality.

The FDA "has long stated that if a drug is anticipated to be widely used in those of childbearing age that it should be studied in pregnancy and lactation around thetime of licensing," Waitt et al. agree. "But in reality this is seldom done."

Compliance with the agency's 2018 guidance, for example, is not a legal requirement so there is little incentive for pharma companies to sponsor studies that include pregnant

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participants, especially since they and other stakeholders — including clinicians, researchers and regulatory bodies — are reluctant to conduct research in what they consider to be a high-risk area in terms of legal liability and ethics, they add.

The guidance also recommends that sponsors include an ethicist in planning such research as well as meet with the appropriate FDA review division early in development to discuss when and how to include pregnant participants. These discussions should also involve FDA experts in bioethics and maternal health.

If a trial participant becomes pregnant during the study, unblinding should occur so the patient may receive counseling on whether the fetus was exposed to the investigational drug, to a placebo or to a control, according to the guidance. The risks and benefits of continuing can be reviewed at that time. Pregnant participants who opt to continue in the trial should undergo a second informed consent process that reflects the additional risk-benefit consideration.

Following the Common Rule and FDA's draft guidance, especially with input from ethicists, can allow sponsors and research organizations to begin enrolling pregnant participants more regularly in clinical trials.

Suitable in pharmacokinetic studies

PK and pharmacodynamic (PD) studies are crucial in pregnant patients. Hormonal and metabolic changes, along with larger volumes of blood distribution, can lower drugs' concentration and weaken efficacy. The best population in which to conduct these studies is pregnant people who are already taking drugs, Diana Bianchi, director of the National Institute of Child Health and Human Development (NICHHD), tells *Clinical Trials Arena*.

Physiological changes during pregnancy can affect the absorption, distribution, metabolism and excretion of many drugs, the University of Utah School of Medicine's Silvia Illamoia and coauthors note in the B*ritish Journal of Clinical Pharmacology*.[10]

For example, reduced gastric acidity, emptying and motility can delay or alter drug absorption, while increased total body water can impact drug distribution. Higher or lower enzymatic activity throughout pregnancy can affect metabolism. And increased renal blood flow coupled with reduced glomerular filtration rate can affect renal excretion. The greatest variability in drug absorption is seen with orally administered drugs, they add.

This becomes especially important when pregnant patients have conditions such as diabetes, hypertension or chronic kidney disease, all of which also can affect drug metabolism, Sewell et al. write.

In addition, fetal and placental development can affect disposition of therapeutics during pregnancy because different gestational stages are associated with different susceptibilities and fetal and placental physiological changes, they say.

Existing FDA guidance on PK studies in pregnant participants acknowledges that little data exists on appropriate dosage and frequency of administration for many drugs during pregnancy.[11] That means that full understanding of PK alterations of drugs when used during pregnancy is lacking.

But ethical and practical restrictions make conventional PK studies challenging during pregnancy and lactation. Any time a drug is administered to a pregnant or breastfeeding woman, concerns arise about potential toxicity to the fetus or infant.

In fact, the guidance notes, "the majority of published PK studies of anti-infective drug products during pregnancy were conducted at the time of abortion or delivery (usually via cesarean section) and were done to determine the transplacental passage of drug."

That means the usual adult dose is typically prescribed for pregnant patients. But the physiologic changes inherent in pregnancy have the potential to result in doses that are too large or too small. The guidance specifies that pregnant patients may be involved in PK studies if:

- Preclinical and clinical studies provide data for assessing potential risks to pregnant people and fetuses.
- The risk to the fetus is not greater than minimal.
- The purpose of the research is development of important biomedical knowledge that cannot be obtained in any other way.

For clinical trials that include pregnant or breastfeeding participants, pharmacometric approaches can be useful for study design and PK analysis, Illamoia et al. write. Such models may use heterogeneous sparse sampling data, which is often all that is available in these populations.

Nonclinical studies to support conduct of trials in pregnant patients, along with clinical data collection to support regulatory decision-making and evidence-based care delivery are necessary, Sewell et al. say.

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Computer models to predict PK in pregnancy could be another tool, Angela Colbers, senior researcher at the Radboud University Medical Center in the Netherlands, tells *Clinical Trials Arena*. While these weren't available a decade ago, their quality in predicting PK changes in pregnancy and fetal exposure is increasing, she says.

Another way researchers can gather PK and PD data is by keeping a person on an investigational drug even if they become pregnant during a trial, Colbers writes. If nonclinical studies have been completed earlier, the data from those could inform participants about the potential risks. They could be included in a separate sub-study and followed in a more controlled setting, Colbers says.

Steps toward inclusion

Improving inclusion for pregnant and lactating patients in the near term will hinge largely on better education for researchers and sponsors about the low liability concerns and what current regulations, including the Common Rule, actually allow, Coffin and Adekar point out.

Better understanding in this area can improve fair inclusion of pregnant clinical trial participants. Fair inclusion should mean that pregnant people who are eligible are not excluded solely for being pregnant and that the research interests of pregnant people are prioritized, "meaning that they ought to receive substantially more attention," Rieke van der Graaf and colleagues at the Netherlands' Julius Center for Health Sciences and Primary Care at the University Medical Center Utrecht explain in *Trials*.[12]

But caution may still be warranted, they say, differing slightly from the recommendations of the NASEM report, which urged the industry to include pregnant patients in diversity, equity and inclusion plans. This concept of fairness does not mean pregnant participants should be included in all or even most research projects, according to Van der Graaf et al. In fact, separate trials in pregnant populations may be preferable once it is known that the effects of a product in pregnant people differ from those in other subpopulations — or once it is known that no such differences exist, they write.

Coffin and Adkar note several ways are available to include pregnant or lactating participants in clinical research that comply with current regulations, such as:

- Minimal-risk research that poses no additional risk outside what the pregnant participant and fetus would face during daily life.
- Retention of trial participants that become pregnant during a clinical trial that excludes pregnant people. The investigator may determine that it is still in the participant's best interest to remain in the study.
- Enrollment of pregnant participants in a study evaluating treatment for a condition that exclusively impacts pregnant patients.
- Enrollment of a pregnant participant in a study evaluating a treatment for a condition not exclusive to pregnancy but that may benefit the pregnant person or the fetus.

A stepwise approach should be used when deciding to include pregnant people in a clinical trial. This should include preclinical, animal model and healthy volunteer data before moving to a clinical trial. Initial clinical trials should focus on patients who require specific medical treatment for their own health. Examples of best practices can be found in preventing mother-to-child transmission of HIV, Waitt et al. write.

To address liability concerns, several legal strategies could be applied to advance inclusion of pregnant people in clinical trials, Sewell et al. write. For example, determining the degree of liability stemming from clinical trials and applying appropriate risk mitigation strategies can alleviate some liability concerns. These could include programs to provide compensation for research-related injuries and to dampen disincentives to including pregnant people in research.

Other options could include incentives, such as public funding opportunities or accelerated regulatory reviews, that could be offered for research that includes pregnant people. Concrete liability reforms and targeted educational initiatives also encourage research in pregnant people, the authors add.

Establishment of large collaborative research networks of clinical trial sites can help improve participation of pregnant trial participants, Illamoia et al. write. These can also provide infrastructure and may facilitate a multidisciplinary approach to improving understanding of PK and PD in pregnant or lactating patients.

Use of big data could also be used to provide insights into obstetric clinical research, Illamoia et al. write. These data are drawn from daily routine clinical practice via EHRs. Studies have shown good correlation between observational studies and clinical trials, they note. For example, the NICHHD has sponsored two such networks: the Maternal-Fetal Medicine

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Unit and the Obstetric Pharmacology Research Unit.

However, use of big data means internal or external validation would be required to confirm their reproducibility and generalization.

Risks and rewards

With the potential for impact on a fetus or infant as well as the enrolled participant, researchers must always conduct a careful risk-benefit analysis. When assessing the risks and benefits to pregnant participants, researchers should avoid looking only at potential risks, Sewell et al. advise. The more potential benefit offered by participation in a trial, the greater the risk that might be acceptable to individual participants.

A related ethical question is whether a responsibility exists to enroll pregnant people in clinical trials, they note, recommending that "researchers should consider the degree to which obtaining adequate evidence for the use of medication in pregnancy or access to prospect of benefit from trial participation raises concerns of justice [and] whether exclusion of pregnant people is appropriate."

IRBs, funders and other stakeholders can support this responsibility by requesting justification for exclusion of pregnant people, they write. Development of a framework or common criteria for adequate justification could buoy such efforts.

Additionally, preliminary evidence during drug development should be scrutinized for any potential safety signals unique to pregnant or breastfeeding patients.

Sponsors and researchers can also apply the "double effect doctrine" to determine when pregnant patients may be included in research, they note. It explains that an act, such as exposure to an investigational treatment during pregnancy:

- Must have good intentions.
- Must exclude any intentional harm.
- Must ensure that the benefit is a product of the treatment, rather than a product of the harm.
- The benefit must be desirable enough that it makes up for any harm experienced.

The doctrine may guide research teams in addressing situations in which a pregnant patient may otherwise be eligible to participate in a clinical trial that could benefit them or their fetus.

Consent and safety monitoring

Consenting takes on additional weight for pregnant or breastfeeding trial participants, Bank notes in the *Clinical Trials Arena* article. When enrolling pregnant or lactating participants, researchers must ensure that consenting materials have all necessary information, including language specific to pregnancy or breastfeeding. Any available information from earlier studies or postmarketing data should be disclosed clearly.

For trial participants that become pregnant during the course of a study, reconsenting to include pregnancy-specific information is necessary.

There should also be a clear plan for safety monitoring, she says, including how to address potential theoretical issues and established procedures for long-term follow up. This information will help patients decide if risks associated with trial participation are acceptable.

This may include extended monitoring of child development, growth and health outcomes for several years after conclusion of a clinical trial that included pregnant participants.

Although safety concerns will always be present when it comes to including pregnant and breastfeeding patients in clinical trials, sponsors and research organizations may soon face growing pressure to include these groups in more studies.

"Safety will always be paramount, but as long as pregnant people get sick (and sick people get pregnant), there will be situations [in which] healthcare can be improved by including pregnant participants in the clinical research setting," Coffin and Adekar conclude. "By including pregnant participants when the risk-benefit ratio is favorable, researchers create opportunities to improve resources for on-label treatment options for pregnant people but also effectively move the "risk" associated with using new therapies out of the clinical setting and into the research setting."

Sponsors and research organizations must meet the requirements of all current applicable regulations. But with proper education about what is allowed within those constraints and use of novel technologies to establish baseline risk-benefit information as well as application of big data techniques to maximize the use of all information that is known, researchers can begin to include more pregnant participants in many clinical trials.

The potential benefits could be huge. With pregnancy- and lactation-specific dosing and administration data sorely lacking for most drugs, research in this area could improve

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healthcare options and outcomes for pregnant and breastfeeding patients.

"In essence, if safety is truly at the heart of this issue, there are times when the safest option may be to include pregnant people in research," Coffin and Adekar say.

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Oncology lessons

1. **Why is oncology research considered a leader in patient-centricity?**
   a. It prioritizes quantitative data.
   b. It prioritizes real-world data.
   c. It incorporates patient-reported data.
   d. It incorporates provider-reported data.

2. **What is one be nefit of patient-centric trials?**
   a. They eliminate participant recruitment costs.
   b. They encourage participant retention.
   c. They do not rely on population health data.
   d. They do not rely on advanced technology.

3. **Which of the following is an example of how technology improves oncology research?**
   a. It reduces the amount of data collected.
   b. It enables continuous real-time data collection.
   c. It eliminates the need for patient involvement.
   d. It increases the focus on clinical outcomes.

4. **Which of the following best describes the role of patient input in patient-centric clinical trials?**
   a. Patients help shape the study's framework.
   b. Patients help shape the study's protocol.
   c. Patients help shape research questions.
   d. All of the above.

5. **True or False: The main focus of oncology research is to extend the life span of patients.**
   a. True.
   b. False.

6. **Which of the following is an example of a best practice in oncology care that other clinical fields have been slow to adopt?**
   a. Oncology specialists commonly discuss clinical trials with newly diagnosed patients.
   b. Oncologists frequently read literature on the latest developments in cancer treatments.
   c. Oncologists actively support narrow research study inclusion and exclusion criteria.
   d. Oncologists regularly publish the results of the patient-generated data they gather.

7. **What is one major goal of precision medicine in oncology research?**
   a. To increase the number of universal cancer therapies.
   b. To improve diagnostic accuracy and treatment selection.
   c. To give greater weight to patient-reported outcomes.
   d. To give less weight to patient-reported outcomes.

8. **Which of the following is a key feature of platform trials?**
   a. They use a fixed protocol.
   b. They use a single control arm.
   c. They consider disease evolution.
   d. They study novel interventions.

9. **Although primarily used in cancer treatments, researchers see promise in using immunotherapy to treat which of the following?**
   a. Cancer comorbidities.
   b. Psychological disorders.
   c. Genetic disorders.
   d. Noncardiovascular disease.

10. **What is one reason for using biomarkers in clinical trials?**
    a. To replace traditional endpoints.
    b. To guide patient stratification.
    c. To exclude overrepresented populations.
    d. To target broad patient populations.

Pregnant participants

11. According to the NASEM report, why have clinical trial professionals traditionally been cautious about including pregnant and lactating participants in studies?
a. Lack of demand for pregnancy-related research.
b. High costs associated with these trials.
c. Safety and legal liability concerns.
d. Difficulty in recruiting pregnant participants.

12. What event is noted as a reason for the hyperprotectionist attitude towards including pregnant participants in clinical trials?
a. The polio vaccine discovery.
b. The thalidomide tragedy.
c. The antivaccine movement.
d. The advent of birth control.

13. What has the NASEM report recommended regarding the inclusion of pregnant and lactating participants in clinical trials?
a. They should only be included if there are no other options.
b. They should always be excluded to avoid risks.
c. The FDA should require inclusion unless there are specific safety concerns.
d. The FDA should require inclusion but only in low-risk observational studies.

14. True or false: Clinical researchers must comply with multiple regulations and laws that specifically forbid including pregnant participants in clinical trials.
a. True.
b. False.

15. Which of the following best describes the best reason to include pregnant people in clinical trials?
a. Doing so can streamline trials and reduce the costs of developing new drugs.
b. Doing so can speed up the approval process for new medications and treatments.
c. Doing so provides evidence-based information for treating pregnant patients.
d. Doing so improves the marketing of new medications and treatments.

16. Which of the following could help researchers predict pharmacokinetic changes during pregnancy?
a. Population health data.
b. Computer modeling.
c. Animal studies.
d. Human trial data.

17. Which of the following is an example of an ethical principle that helps determine when pregnant participants may be included in clinical trials?
a. The double-blinding effect.
b. The random-sampling decree.
c. The double-effect doctrine.
d. The placebo-control tenet.

18. Why is the exclusion of pregnant and lactating patients from clinical trials problematic, according to the NASEM report?
a. It increases costs, decreases efficacy and delays approvals.
b. It leads to incomplete dose, efficacy and safety information.
c. It reduces the sample size of clinical trials.
d. It increases the sample size of clinical trials.

19. What kind of studies does the Common Rule require before enrolling pregnant participants in a clinical trial?
a. Observational studies to gather evidence.
b. Preclinical and clinical studies to assess risks.
c. Randomized studies.
d. Animal studies.

20. Which of the following recommendations is included in the NASEM report?
a. Sponsors should independently determine the safety of pregnant participants due to a lack of regulatory guidance.
b. Congress should pass legislation to incentivize labeling information for pregnant and lactating patients.
c. Researchers should complete studies of other populations before recruiting pregnant participants.
d. All of the above.