RESEARCH PRACTITIONER

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25 Years

Evidence-based research: Systematic reviews reduce waste, build consensus

by Mike Ingram

Within the clinical trials industry, there is a growing consensus about the value of evidence-based research — that is, research that more carefully and methodically takes into account past studies on the same topic — as a way of more efficiently building clinical consensus around particular therapies and to fight what some see as rampant waste and redundancy in research.

Over the past two decades, a slew of meta-research studies has suggested that up to half of all clinical research is unnecessary, either because it's based on research questions that have already been settled by prior studies or because it doesn't fully take into account patients and practitioners.

In the first of a three-part series on evidence-based research published in the *Journal of Clinical Epidemiology*, Karen Robinson, who is affiliated with the Johns Hopkins Evidence-based Practice Center, notes that this research waste isn't just an economic problem, but an ethical one.[1] "Lack of consideration of prior research assessing the same

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Learner Outcomes:

1. Define evidence-based research and systematic reviews.
2. Explain the consequences of failing to conduct systematic reviews.
3. Give examples of how evidence-based research can improve research quality.
4. Discuss the challenges of conducting systematic reviews and how to overcome them.

Biostatistics, bioinformatics intersect to produce well-designed trials and robust data

by Elizabeth Tilley Hinkle

In clinical research, appropriate use of biostatistics is crucial to a successful trial. Biostatistical methods determine the appropriate size and type of study population, underpin the entire statistical analysis plan (SAP) applied throughout the trial and play a key role in ensuring the integrity and quality of data generated during the study. This helps ensure that PIs and other key research staff draw the right conclusions about an investigative treatment's performance based on the evidence provided.

But clinical research staff may not always fully understand or appreciate the full scope of how biostatistics — and the related area of bioinformatics — contribute to the design and execution of clinical trials. Biostatistical analysis is applied to identify the appropriate population size and type for a clinical trial, for example, which affects inclusion and exclusion criteria. And the specific questions each study investigates requires customized biostatistical analyses to ensure that the data provides answers to those questions, according to information on the University of Cincinnati (UC) College of Medicine website.[1]

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Learner Outcomes:

1. Explain the benefits of biostatistics and bioinformatics in clinical trials.
2. Define the roles of bioinformatics specialists and biostatisticians in clinical trials and distinguish between the two.
3. List specific tasks these statisticians perform throughout all phases of a clinical trial.
4. Describe how these specialists contribute to the overall success of clinical trials.

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Exam for this issue is available to complete until: Mar. 1, 2025

Estimated time to read issue and complete exam: 3.0 hours

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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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Regulatory Update

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FDA Updates Advice on COVID-19 Drug Trials in Final Guidance

The FDA has offered its latest recommendations for sponsors of drugs being developed to treat or prevent COVID-19, issuing another straight-to-final guidance on clinical trials that supplants the agency's prior direction on the subject.

The 19-page guidance, which does not cover long COVID-19 treatments, preventative vaccines or convalescent plasma, pertains to phase 2 and 3 trials and focuses on trial populations, trial design, efficacy endpoints, safety considerations, and statistical considerations.

The bulk of the new guidance covers COVID-19 treatment trials and their populations, designs, conduct, efficacy endpoints and safety/statistical considerations.

In addition, the FDA reiterated the importance of enrolling diverse study populations and notes that this latest guidance can be used to inform COVID-19 drug development for children and pregnant/lactating patients.

Although the FDA issued the guidance without industry comments, industry may still submit feedback.

Read the full guidance here.

FDA Finalizes Numerous Guidances, Issues New Master Protocol Draft Guidance

As 2023 drew to a close, the FDA issued several final guidances, including documents on collecting trial data with digital health technologies, developing rare disease drugs and biologics, and using real-world data sources, as well as a new draft guidance on clinical trial master protocols.

Master Protocols for Drug and Biological Product Development

The new draft guidance includes many principles of the FDA's May 2021 guidance on master protocol trials for COVID-19 treatment and prevention, which expired at the declared end of the public health emergency in May 2023.

The draft expands the application of those principles into other therapeutic areas, offering advice on designing and analyzing clinical trials conducted under master protocols, focusing on randomized umbrella and platform trials across a range of therapeutic areas.

Included are recommendations on randomization, control groups, informed consent, blinding to treatment assignment, adaptive design challenges, multiplicity, comparisons between drugs and safety, in addition to considerations on trial oversight, data-sharing and information dissemination.

Comments on the guidance are due by Feb. 22, 2024.

Read the guidance here.

Rare Diseases: Considerations for the Development of Drugs and Biological Products

Some major changes from the February 2019 draft version include:

- New sections (safety considerations, pediatric considerations and participation of patients and patient groups in drug development programs)
- New considerations for nonclinical studies
- Information on using external controls and early randomization
- Information on changes to drug substance and manufacturing processes
- The removal of the natural history section, with reference to a separate March 2019 draft guidance.

Read the guidance here.

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Clarifying the meaning of digital health technology (DHT) functions, this final guidance, based on the December 2021 draft, provides further explanation of DHT regulatory considerations and now includes references to Form FDA 1571 and Form FDA 356h for tracking submissions that include DHT data as well as:

- Revisions to the section on conducting verification, validation and usability evaluations
- Clarification on protecting and retaining DHT records
- Clarification on sponsor and investigator roles regarding DHTs
- Additional recommendations on managing changes to DHTs during clinical trials, including updates to hardware/software and new models/versions

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- Various editorial changes intended to improve clarity

Read the guidance here.

Data Standards for Drug and Biological Product Submissions Containing Real-World Data

With its finalization from the December 2021 draft, the guidance is now clearer on the FDA's perspective on challenges to using currently supported data standards for real-world data sources.

The document also includes more detail on available FDA resources on the use of data standards for submitted trial data.

Read the guidance here.

Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products

This final guidance has seen considerable changes from its November 2021 draft. For example, sponsors intending to use registry data in their drug and biologic submissions are responsible for making sure the registry's characteristics support the collection of relevant and reliable data, including when the data are from a registry not managed or designed by the sponsor.

The FDA also expects sponsors to have access to the registry data's metadata, the guidance notes.

Read the guidance here.

PI Warned for Failing to Stick to Treatment Phases, Maintain IRB Approval

A Detroit, Mich.-based principal investigator's (PI) failure to renew IRB approval during a trial and adhere to the required treatment phases in a trial's investigational plan has netted an FDA warning letter.

The letter, issued to Jeffrey Taub, a doctor specializing in hematology and oncology at the Children's Hospital of Michigan, outlines two violations,

one of which specifically involved a pediatric patient, as well as the agency's requests for greater details on corrective actions.

The first, a failure to ensure that the trial was carried out according to the investigational plan, centers on a six-year-old participant who was mistakenly allowed to continue receiving the investigational treatment past the cutoff point, resulting in extra doses and additional five-day cycles. This mistake put the participant at a higher risk of serious toxicities that included neurotoxicity and hematologic toxicity, according to the agency.

Taub's written response acknowledged the error, assigned blame to a sub-investigator who misunderstood the drug administration plan and said the IRB was alerted by its deadline. It also stated the participant would be monitored according to the protocol during each remaining study visit for any related adverse events or toxicities and noted four follow up actions taken at the site.

This response, however, lacked important details, the FDA said, including information on the policies and procedures the site would implement to ensure compliance. And because of the gravity of the issue, the agency requested documentation surrounding these policies and procedures, including randomization assignments.

The second violation, a failure to ensure continued IRB review and approval of trial conduct, centers on a trial's IRB approval that lapsed from Jan. 14-24, 2022. Despite this, the study treatment was dispensed to a participant and bone marrow and peripheral blood specimen samples were gathered from a participant during this time period.

This issue, the PI said, stemmed from "a multitiered review of the continuing review, which delayed the continuing review from being addressed at a timely, regularly scheduled IRB meeting, as well as to staff turnover after submission of a continuing review."

Additionally, he noted the study had been reapproved and study staff responsible for continuing reviews would begin receiving 30-, 60- and 90-day email reminders before study approval expirations in addition to receiving retraining. As part of this latter strategy, study staff would initiate the continuing review process at the 90-day mark to allow for submission prior to the 30-day reminder.

Again, the FDA did not find this response sufficient and sought more details.

"For example, you did not provide sufficient details about the policies and procedures you would institute at your site to ensure submission of IRB continuing review before study approval expiration dates, including procedures regarding email notifications at 90, 60 and 30 days before the date on which the study's approval expires," the agency said. "Without this information, we are unable to determine if your corrective action plan is adequate to prevent similar violations in the future."

Read the full warning letter here.

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clinical question has meant that thousands of patients over many years have been recruited to clinical trials well after the intervention was proven to be effective or not effective," Robinson and her coauthors write.

In 2007, for example, after multiple studies showed that the use of statins was effective for patients with coronary artery disease, both the American College of Cardiology and the European Society of Cardiology published official clinical recommendations to that effect. Still, according to a 2021 *Polish Archives of Internal Medicine* article, between 2008 and 2019 there were more than 2,045 original randomized clinical studies or protocols addressing this same clinical question.[2] "More alarmingly," writes Hans Lund of the Section for Evidence-Based Practice at the Western Norway University of Applied Sciences, those unnecessary studies sorted 101,486 patients into control groups that were not treated with statins. As many as 550 of those patients died and another 973 experienced a new or recurrent myocardial infarction. Another 161 suffered a stroke.

"Most of these major adverse cardiac events could have been prevented as the clinical guidelines clearly recommended treatment with statins for these patients," Lund and his coauthors, including Johns Hopkins' Robinson, write.

In another example, Lund et al. point to the use of intravenous streptokinase as thrombolytic therapy for acute myocardial infarction, which by the mid-1990s was backed up by solid evidence from eight clinical trials. In the years that followed, however, more than 25 additional studies were performed "with no effect on the results except to narrow the confidence level." These 25 studies enrolled 34,542 patients, including 17,271 in control groups who may have therefore been denied an effective, well-studied treatment.

One solution to these problems, according to proponents of evidence-based research, is for researchers to use systematic reviews of existing studies to determine whether or not new research will actually contribute new information.

"Redundant studies could be avoided if clinical researchers considered prior similar studies in a systematic and transparent way when preparing a new study," Robinson et al. argue. In some cases, those systematic reviews may already exist. In other cases, researchers may need to perform their own systematic reviews or hire firms that specialize in the practice. Either way, these reviews can help researchers identify gaps in the existing literature and better craft research questions that have yet to be satisfactorily answered.

Yet the vast majority of researchers embark on their own studies without first conducting a thorough review of the existing literature, several meta-studies have found.

Moving toward systematic, transparent, relevant research

A 2022 analysis published in the *Journal of Clinical Epidemiology*, for example, found that the practice of conducting systematic reviews to inform the design of new studies "varies considerably."[3] Across the studies in the analysis, 0 to 73 percent of study protocols were influenced by an analysis of past research; the mean was 17 percent. The authors noted that the wide variety was in part due to a handful of studies that were funded by the UK's National Institute for Health Research Health Technology Program, which requires researchers to conduct and explicitly reference systematic reviews.

"It is clear that there is room for improvement in the implementation of evidence-based research," the authors write. "Research redundancy due to the wrong questions being asked by scientists, poor study design, inaccessible research, and selective and biased reporting is not only a matter of redundant trials with no obvious value for research, practice or the end user, but is also a matter of irresponsibility towards funding resources and risks damaging the public's trust in research."

One solution is for researchers to use systematic reviews of existing studies to determine whether or not new research will actually contribute new information.

The authors do acknowledge that there are barriers to evidence-based research, including the work and time it takes to conduct a systematic review and a lack of education among researchers, but add that these are hardly insurmountable burdens.

A similar 2022 analysis led by Jane Andreasen of the Aalborg University Hospital, Denmark's public health and epidemiology group, looked at 3,621 original studies and protocols — culled from meta-studies published since 2015 —

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and found that fewer than half (48 percent) used systematic reviews to justify their research questions and study designs.[4] Of the studies that did cite such reviews, there were still a number of frequent problems, such as studies that mentioned certain relevant systematic reviews but excluded others without clear justification for doing so.

Andreasen and her coauthors also note that some systematic reviews are not methodologically sound, which can present an additional challenge for researchers. A poorly designed or executed systematic review, they argue, can have ripple effects for future research.

In a 2022 review, Lund et al. found that "researchers hardly ever use a systematic and transparent approach when planning and interpreting new studies."[5] While most studies made nods toward past research, they found the approach was often opaque, suggesting that researchers were cherry-picking the past data they relied on when planning and contextualizing their own studies.

"It is unclear why researchers, who had been trained to be systematic and transparent in everything they do while performing research, are not being similarly systematic and transparent during the planning and interpreting phases of the research process." One potential cause, the authors speculate, could be "a lack of knowledge of the problem," requiring more education of researchers in the principles of evidence-based research.

The authors of the *Polish Archives of Internal Medicine* article strike a befuddled tone that these systematic reviews aren't already standard practice.

Most researchers "would accept that research is a cumulative enterprise, meaning any new study always builds upon existing knowledge," Lund et al. write in the 2021 article. "But something else is going on. Several studies clearly indicate that the decision of which prior research studies to cite is not based upon a systematic and transparent approach but rather influenced by personal preferences and strategic considerations."

For example, the authors point to interviews conducted with 87 research scientists about their decisions to select specific citations to include in their own studies. None of the researchers indicated they'd included those citations based on a thorough, transparent review of all the available literature.

Instead, 24 percent of respondents said they'd selected a given citation because the author was known to them, while 15 percent said the cited study was considered eminent in their field. Another 10 percent said they selected a given study because they were familiar with the journal in which it was published or the conference at which the paper was presented. Other reasons included citing a source that used methods the researchers considered sound, familiarity with the sponsoring institution or research group and that they'd conducted the research themselves.

Other meta-studies have found that study authors tend to cite positive and supportive prior studies at much greater rates than they cite negative, critical or nonsignificant research. "In other words, authors of scientific publications do refer to earlier research, but this is very rarely done systematically or transparently," the authors note.

Moving away from bias, waste and redundancy

Evidence-based research isn't a new concept — if anything, its core tenets are at the heart of the scientific method as it's been understood for centuries — but in recent years, calls for widespread adoption have increased, with some journals and funding agencies now requiring researchers to follow certain of its principles. That push really got going around 2014, when Lund and several others founded the Evidence-Based Research Network (EBRN), which has led the charge on educating researchers and funding organizations about the issue of research waste and has championed systematic reviews.

In 2016, Lund and several colleagues published "Towards Evidence-Based Research," in *BMJ*.[6] In that article, they note that the National Institute for Health Research in the UK had begun requiring applicants for primary research funding to reference a current systematic review in their application and encouraged other organizations and journals to follow suit. They identify two specific aims of the EBRN: no new studies without adequate systematic review of existing evidence showing that the new research is justified; and more efficient production, updating and accessibility of systematic reviews.

That second aim, according to the *BMJ* article, was a particularly important component of ensuring the first. While the number of systematic reviews had increased sharply in the preceding years, researchers still risked relying on reviews that were either out of date or of suboptimal quality.

"Alternatively, a lack of common measures and definitions in included studies may preclude a statistical synthesis of results, making it difficult to integrate new results," according Lund and his coauthors. And information specialists and librarians play an especially important role in this regard in

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helping researchers find and analyze appropriate systematic reviews and helping to train the next generation of researchers in evidence-based methods.

Also in 2016, Lund and the EBRN prepared a white paper for the European Commission calling for more evidence-based research methods.[7] "One way to diminish redundant and unnecessary research would be if funding agencies demanded that the applicants used systematic reviews to justify and design their new study." They also provided an official definition of evidence-based research, which is still frequently cited today: "the use of prior research in a systematic and transparent way to inform a new study so that the research is answering questions that matter in a valid, efficient and accessible manner."

In their white paper, they sum up some of the biases they found in reviewing the way researchers cited prior studies, including papers from high-impact journals being cited more frequently than those in low-impact journals and articles by high-prestige authors being cited more often than lesser-known authors.

"One of the key characteristics of science is the cumulative way in which knowledge develops," they write. "To be systematic and transparent, the authors of a systematic review must include all studies fulfilling the inclusion criteria, not only those that suit the authors or bolster their agenda."

Traditionally, researchers formulate research questions based on their personal interests and ambitions, along with their existing clinical knowledge, Robinson et al. write in the *Journal of Clinical Epidemiology*. An evidence-based approach doesn't require researchers to abandon those factors when setting a research question, but to add two other factors: a systematic and transparent review of the existing evidence and ensuring the research question considers the impact on patients and practitioners.

"Thus, the evidence-based research approach acknowledges the importance of researchers' own context," they write, "but emphasizes that a systematic synthesis of earlier similar studies and a similar synthesis of end users' perspectives must be added to avoid irrelevant and redundant studies."

Using evidence to strengthen studies, advance knowledge

Robinson et al. also explain that an evidence-based approach should ideally inform all phases of research. The systemic review should be conducted during the pretrial phase and used to determine whether the research question is justified. That review can also shape the study's design, including the specific investigative question and the patient population the researchers propose to enroll.

After the study is conducted, the results should be put into context with prior research. That includes updating the existing systematic review, evaluating the new study's contributions to the existing research and thinking through the study's implications for both clinical practice and future research. If the study's results are strong enough, they can be used to inform clinical practice and ensure no future redundant studies are conducted. If the results are more ambiguous, they can point to specific areas for future research.

In the second article in its three-part series, the *Journal of Clinical Epidemiology* dives deeper into how to best conduct a systematic review and how to use that review to shape a prospective study.[8]

At its base, the goal of the systematic review is to determine whether there is value in the proposed new study. If the review determines that previous studies have supplied enough unambiguous evidence on the proposed research question, the study should either be abandoned or revised. "Only if the researchers can clearly demonstrate that the intended study will add value — that is, there is both a societal need for it and it will fill a shown evidence gap — should a new study be planned and designed in more detail."

In some cases, the authors note, existing systematic reviews may exist, in which case they can be reviewed by the researchers. For example, Cochrane.org maintains the Cochrane Library, a collection of databases that contain high-quality, independent evidence to inform healthcare decision-making. The library publishes and tracks systematic reviews. More recently, the International Collaboration for the Automation of Systematic Reviews has been doing work to increase the speed and efficiency of the systematic review process.

The number of globally published systematic reviews has been growing rapidly, they write, meaning that in the future, "health researchers will have a higher chance to identify and use existing systematic reviews for justifying and designing their new study." The bad news, however, is that the proliferation of systematic reviews has also led to a number of irrelevant or redundant reviews, "making quality appraisal even more important."

Generally speaking, a systematic review can be problematic if it's either out of date or based on poor quality analysis.

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While there's no universally accepted standard for how old a systematic review can be and still be considered relevant, the authors of the *Journal of Clinical Epidemiology* series argue that reviews older than five years should likely not be relied on, at least not without additional searching to update them. A more precise threshold, they suggest, should be based on an assessment of the specific clinical field and the speed with which evidence in that field tends to evolve.

If no relevant and adequate systematic review exists, the researchers must prepare their own or outsource that task to experts in the preparation of systematic reviews.

But how do researchers interpret the results of a systematic review? Experts suggest they consider three elements: the ethical element; the quality grading of the evidence found in the systematic review; and the use of statistical methods to support the decision-making process.

In terms of ethics, the *Journal of Clinical Epidemiology* authors suggest two questions to guide whether a new study is ethically supported:

- Is the research question scientifically valid and not a trifling hypothesis?
- Will it be possible to generalize the new results beyond the sample and context of the study?

Beyond the ethical questions, researchers should evaluate the strength of the existing studies and the confidence level in their conclusions. A number of well-tested statistical methods can be employed in this analysis, the authors note, including confidence intervals, prediction intervals and trial sequential analyses. "To sum up, one can be fairly confident that a new study [should] be carried out if the answers to the two ethical questions are 'yes,' if the grading of the evidence for the conclusion from the systematic review indicates that the certainty of the evidence is low or very low and if statistical methods support low certainty of evidence." The final decision, the authors state, will come down to a nuanced consideration of the existing evidence, the relevance of the topic and the opportunity cost of the research.

An evidence-based approach doesn't just rely on a review of the existing evidence. Rather, it relies on meaningful engagement with end users, which would generally include patients, clinicians and caregivers. In many cases, patients and caregivers may be represented by national organizations. Likewise, clinicians are often represented by national or international professional organizations. These can be important points of contact when designing a study. "Numerous studies show a discrepancy between what end users need and what researchers focus on, indicating that researchers are very poor at identifying the needs of end users when planning new research." In the past 20 years, an increasing number of research funders and regulators have begun to require the involvement of end users in research, the authors note.

In a 2021 article for the journal *Research Involvement and Engagement*, Ormstad et al. advocate for what they call "the bridge-building model," which seeks to connect evidence-based practice, evidence-based research and public engagement.[9] "The mismatch between the research preferences and priorities of patients and clinicians on one hand, and those of researchers on the other, has encouraged more patient and public involvement in research in general and in research priority-setting," they write. New research, they argue, "should be designed to answer both quality-assured evidence gaps as well as the needs and priorities from users and society."

For too long, Ormstad et al. write, priority-setting for clinical research has been exclusively the domain of researchers and their funding bodies. This has sometimes led researchers to focus more on work that is likely to be cited by others — an important metric for academic researchers in particular, who tend to be rewarded for research with "high impact" — than on what will best help patients and health professionals.

Those patients and health professionals should ideally have input in the process of developing research questions and the design and delivery of the study, Ormstad et al. argue. On the one hand, this is a practical suggestion — a way to improve research by ensuring it will have practical, clinical utility. On the other hand, there is also a moral component, they state. "The moral argument advocates that involvement is a right because citizens should have a voice in publicly funded research simply based on the saying, 'nothing about me without me.'"

As early as 1991, they note, the UK National Health Service was beginning to recognize the importance of involving a variety of stakeholders in research planning. The UK Clinical Research Network, in particular, developed a number of guidance documents and toolkits for researchers to that end. By 2020, they stated, there was a "rich landscape" of networks and organizations worldwide advocating for this kind of patient and practitioner involvement. "What tends to occupy people now is methods that involve people in authentic and meaningful ways, achieving diversity and inclusion

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in involvement and assessing the impact and effect of public involvement in research."

Ormstad et al. use the term "needs-led research" to denote clinical studies that take the needs of patients and practitioners into account in meaningful ways. As an example, they highlight the recent work of the Kavli Trust, a Norwegian funder of health research that in 2017 launched a new initiative aimed at reducing research waste and aligning research with the needs of specific patient populations. Based on the Kavli Trust's own evaluation of existing research grants and disease patterns in Norway, the organization decided to fund research targeting selected evidence gaps within the field of childhood and adolescent mental health. These evidence gaps were identified via a two-step process. First, experts identified actual evidence gaps throughout comprehensive literature searches. Second, patients, caregivers and mental health professionals were asked to prioritize those evidence gaps. Their eventual call for research included the top 10 evidence gaps and required applicants to address one or more of the 10 when seeking funding. As of late 2021, 10 ongoing research projects have been funded.

The authors also highlight the work being done at Oslo Metropolitan University, where doctoral degree students are now specifically trained in how to involve end users when selecting and developing a research question. That work isn't merely theoretical: The students are then using actual end user input to shape their own research questions. "This represents a considerable change" in how graduate students choose their research subjects, the authors note. The projects are based in hospital settings, such as intensive care, stroke management, maternity care, and community-based settings, such as elder care and services for children and youth. In a number of cases, the same patients who provided input into the shape of a given study are able to actually participate in the study.

Those projects are particularly good examples of needs-led research, Ormstad et al. contend, because the involvement of patients and clinicians is significant and meaningful. "It is important that the user involvement process is not tokenistic, whereby the researchers have already decided what their research questions will be and are not open to comment or critique," they write.

In the third article in its series on evidence-based research, the *Journal of Clinical Epidemiology* turned its focus to what happens after a research study is completed and how to ensure the results are put into the proper context with prior research.[10] "A single study can very rarely (if ever) provide a definitive answer to the question investigated. Therefore, placing the new study in the context of relevant previous research is key. Meta-research has shown that the interpretation of new results is at high risk of being biased if only a subset of earlier studies is included in the discussion of these new results," according to the article.

Rarely, however, do researchers put their findings into the proper context, the authors, again led by Lund, found. Instead, the focus tends to be on the point estimate and confidence interval of the new study in isolation.

This is another reason why a systematic review is so important, they write. If such reviews are consulted prior to the new study, it would be much easier to revisit and update those reviews after the study is completed. "Identifying or preparing a systematic review during the planning phase of the new study will considerably lessen the required work when aiming to place results in context."

Once a study is completed, researchers should assess the effect of adding the new results to the existing systematic review and determine whether the new data affects the conclusion or the level of certainty in the aggregate. As an example, they point to a study on the effects of taxanes as adjuvant chemotherapy for patients with early-stage breast cancer, which was undertaken in 2000. At that time, only a few studies had presented initial results. But by the time the researchers were preparing to report their own results in 2009, a systematic review on the topic had been published by Cochrane Library. The researchers reviewed this and another systematic review and updated the results of those meta-analyses with data from their own research. "Thus, when discussing the impact for future clinical practice and research, the key findings included not just the results from the new study alone but a much more meaningful estimate and conclusion based on the combined results of all studies examining the same clinical question."

Once this synthesis of results has been performed, the next question to ask is whether it's possible, through an analysis of the combined data, to draw a definitive conclusion or if further research is required. If a definitive conclusion can be drawn, the second question is whether there is enough confidence in this conclusion, that is, whether the evidence is of sufficiently high certainty. If so, the authors of the new study can likely recommend that no further research into the particular question is required.

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Either conclusion should be included in the study findings, along with recommendations for clinical practice, according to the *Journal of Clinical Epidemiology* authors. "We recognize that numerous factors must be considered when evaluating the implications of a new study for both clinical practice and research," they write, "but we want to stress the role of the evidence-based research approach as a vital step in this process."

If the certainty of the cumulative evidence is either unclear or low, reporting that fact can help guide future research and mitigate against the premature adoption of a therapy into clinical practice. If, on the other hand, there is a high degree of certainty, clinicians can use the results in their own decision-making and researchers can avoid unnecessarily redundant research into the same question.

Understanding the challenges of evidence-based research

The emphasis on systematic reviews in the past decade or so has made these reviews much more prevalent, but this has begun to cause its own issues of research waste, according to a 2023 commentary by Puljak and Lund.[11] In fact, the issue of unnecessary redundancy in systematic reviews has reached "epic proportions," they write. However, they note, not all duplication is bad. Replication in research is an important way to discover flaws or shortcomings in past research efforts.

The problem is that there is no clear standard, as of yet, for how much redundancy in systematic reviews is too much.

In fact, Puljak and Lund note, there isn't even a consensus definition of what constitutes a "systematic review," which is another underlying problem. "Multiple organizations and authors have provided definitions or characteristics of systematic reviews, but the analysis of those definitions and characteristics showed that they are heterogeneous and often vague in their defining characteristics," they write. For example, a definition may stipulate that a systematic review should include a "systematic search" of the existing literature, but without any further details about what characteristics would make the search systematic.

Without a set of minimum criteria to define such a review, they write, "anything can be self-described as a 'systematic review,' even though the review may not adhere to minimal methodological expectations, such as properly searching multiple sources."

This also makes it hard to define a redundant systematic review, since such a definition would naturally hinge on whether those prior systematic reviews were actually worthwhile. Even if the prior systematic reviews are acceptable, there is no "magic number" for how many subsequent reviews should be performed before they are considered redundant. Most people, the authors state, would likely consider two or three systematic reviews on the same topic and with similar eligibility criteria and outcomes to be reasonable, while four or more would generally be seen as excessive.

Puljak and Lund draw an important distinction between clinical trials and systematic reviews. A redundant clinical trial, as already discussed, can be harmful to study participants who may miss out on a treatment that has already been well-proven, while a systematic review doesn't involve human subjects. However, too much redundancy and overlap still leads to wasted effort and resources that could have been better allocated to other research efforts.

They suggest that researchers only take on duplicative systematic reviews when the existing review used inadequate methods or had some other flaw or if it's old enough to require an update. In those cases, they suggest reaching out to the original authors to make sure they don't have an updated version already in the works. Otherwise, a "veritable tsunami" of systematic reviews and meta-analyses could drown researchers, clinicians and public health officials, leading to distrust or skepticism about systematic reviews in general.

The most important step, however, is to arrive at a consensus definition of what makes something a systematic review, they argue.

"If we could adopt a clear, detailed consensus definition of a systematic review with minimal methodological standards that a systematic review should adhere to, we could focus our efforts and considerations only on studies that meet that criteria," Puljak and Lund write. "Then, it could become apparent that many 'redundant systematic reviews' are actually not systematic reviews at all."

Furthermore, if researchers could settle on a definition of "conclusive" research, it would be easier to declare that certain research topics should be closed and that further primary or secondary research on the topic is not necessary, they add. After all, reducing unnecessary research waste is the whole point of systematic reviews — and evidence-based research more generally — in the first place.

Another problem that's been identified with existing systematic reviews is that too often they include old trials that can skew the intervention effect. In a 2022 article, Smail-Faugeron et al. dive into the debate over whether a systematic

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review should cut off included studies at a particular date.[12] They note that the nonprofit Cochrane, which also advocates for systematic reviews and offers online and live training, generally recommends against date restrictions, unless it's already known that relevant studies could only have been performed after a certain date, such as with an intervention that only existed after a certain point in time. Because of this general advice, Smail-Faugeron et al. found, there are systematic reviews that include studies performed up to 50 years ago.

Including such dated research raises a number of concerns, they argue. Major changes may have occurred in clinical practice, patient management and the characteristics and conduct of clinical trials. "All these changes may limit the generalizability of older trial results and may affect the intervention effect itself," they write. In their own analysis, they attempted to determine whether that was indeed the case.

Their analysis found that in systematic reviews that included older clinical trials, those older trials "showed significantly larger intervention effects on average than did recent trials." They also found a number of Cochrane reviews that included trials from before 2000, likely because of the way these reviews are regularly updated, so that new studies are added rather than performing an entirely new systematic review.

These older studies may disproportionately skew the intervention effect for a number of reasons, they conclude. First, standard-of-care improvements over time could lead to reduced effect of the treatment relative to the accepted standard. Second, components of the treatment could have become standards of care themselves over time based on those earlier studies. Third, older trials have tended to show a higher risk of bias than more recent trials, largely due to improvements in clinical trial conduct.

In the end, there should be standards for the age of studies to be included in systematic reviews, but this standard would likely be topic-specific, rather than a one-size-fits-all approach across all clinical research subjects.

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Biostatistics and bioinformatics often are treated as a single entity in the life sciences arena. But the two are distinct fields, albeit closely interrelated ones. "Bioinformatics is more concerned with the development of computational algorithms for data analysis," according to a post on Cromos Pharma's website. "Simply put, bioinformatics deals with copious amounts of disparate data points, whereas biostatistics works with a smaller volume of data."[2]

Specific definitions of the two can vary across different sponsors and research organizations. But there is general agreement on what each field entails. Generally, bioinformatics focuses on the analysis and interpretation of datasets, often involving development of software tools to aid the management and analysis of large, complex datasets, according to UC.

Meanwhile, biostatistics in clinical research is concerned with designing, conducting, analyzing and interpreting data generated during clinical trials, according to Yoh, a technology and life sciences recruiting firm.[3]

In other words, while biostatistical methods can be used to meet a variety of goals — such as identifying biomarkers and predicting responses to investigational products — bioinformatics is focused on developing methods and computational tools to aid in understanding complex biomedical data.

In the life sciences industry, including in clinical research, bioinformatics is also responsible for developing and applying algorithms and analysis methodologies to large collections of medical data, such as that gathered during a clinical trial, according to Yoh.

Biostatistics permeates clinical trials

No clinical trial can be successful without properly applied biostatistics. "Biostatistics is a cornerstone of clinical research, playing a pivotal role in study design, data analysis and regulatory compliance," according to ICON, a CRO. "Biostatisticians ensure the integrity and quality of clinical trial data, helping researchers draw valid conclusions and make evidence-based decisions."[4]

One factor underlining the importance of biostatistics is the continually growing complexity of clinical trials, with studies collecting, compiling and analyzing more safety monitoring data to meet regulatory demands, Supreet Kaur Gill et al. write in a recent issue of *Perspectives in Clinical Research*.[5]

The Tufts Center for the Study of Drug Development (CSDD) notes that the typical phase 3 trial during the 2016-2021 period had an average of 28.5 endpoints, a number that's likely to rise.[6] And the average number of research sites per trial rose substantially for both phase 2 and 3 trials during the same period.

The result is that the amount of data generated during clinical trials has been increasing dramatically in recent years, with no sign of slowing down. Adding in disparities in how data may be collected during a clinical trial makes the management, organization and analysis of data a massive undertaking that requires highly customized solutions.

The tasks most often associated with biostatistics in clinical research happen after data analysis is finalized, Antonia Zapf et al. write in *BMC Medical Research*.[7] Biostatisticians carry most of the responsibility for correct interpretation and appropriate presentation of study results.

Data analysis technologies are advancing at a record pace. Biostatisticians use visualization techniques to help provide insights into study progress and data quality, especially when electronic data capture and management tools are in play. This helps detect erroneous data and outliers, often in real time, thus allowing for early intervention, according to ICON.

Using those techniques, biostatisticians play a key role once data is collected, when they apply advanced statistical methods to analyze and interpret the results of the trial. Techniques may include hypothesis testing, regression analysis and survival analysis.

They also are responsible for ensuring that analytical methods comply fully with regulatory requirements and industry standards.

Biostatistics enable research staff to quantify and analyze clinical data. Statistical analysis is used to establish causality, measure treatment effectiveness, model disease progression and more. Without biostatistics, the evidence in evidence-based medicine simply wouldn't exist, according to a blog post by Clinvigilant, a CRO.[8]

"High-quality data is crucial for sound biostatistical analysis," Clinvigilant notes. "Great care must be taken in designing data collection protocols, safeguarding against missing or inaccurate data and 'cleaning' data prior to analysis."

Biostatisticians also monitor and analyze interim data during the trial. If the study design must be modified during the trial — such as changes within an adaptive design or early termination after an interim analysis — biostatisticians can help manage data during that shift.

Once a study is closed, biostatisticians provide key contributions to the results in the study report and publications submitted to medical journals. Biostatisticians often write

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the statistical part of the clinical study, according to clinical research consultant Credevo.[9]

Selecting the ideal sample size

While the bulk of data analysis is performed after all data is collected, statistical methods must also be part of the study protocol, which means they must be selected during the planning phase, according to Zapf et al.

The responsibilities of biostatisticians extend from the planning phase through execution of a clinical trial to data analysis and publication of the results. They arguably contribute the most during the study planning period, contributing key analytical planning expertise that can be essential to ensuring valid study results, the authors write.

Perhaps the most well-known job of a biostatistician is calculation of the right sample size for the clinical trial. This requires evaluation of several factors that influence the size of the study, timelines and budget requirements, Credevo notes.

Sample size is a vital component of the study design that requires biostatistical evaluation, Haidy Effat, associate professor of pharmacology and toxicology at Ain Shams University, writes for *Editage Insights*.[10] While "a tiny sample can lead to underpowered research with inconclusive results, an excessively large sample is a waste of time and resources," he writes.

"The primary goal of biostatistics in clinical trials is to ensure that the sample size is adequate to draw valid conclusions, minimize bias and account for variability in the study population," according to ICON.

Biostatistics are applied to identify the population with characteristics that fit the clinical trial's parameters, Jordan Elm of the Medical University of South Carolina's Department of Public Health Sciences explained in a National Institutes of Health seminar.[11] These include:

- The proportion of the target population that experiences the specific signs and symptoms the treatment aims to address;
- The proportion of that segment that will respond favorably to the investigational intervention; and
- The mean volume of response.

This information identifies the parameters used to identify potential clinical trial participants and to develop inclusion/exclusion criteria.

"The distinction between statistics and parameters is essential to the understanding of statistical inference," Elm says. "Parameters are constants, while sample statistics are random variables. The values of parameters do not change from sample to sample, whereas statistics change whenever the population is resampled."

Biostatistics help shape statistical analysis plan

When considering the use of biostatistics in clinical trials, most research professionals immediately think of determining the appropriate sample size for enrollment and establishing statistical analysis methods for a protocol, Jody Ciolino et al. write in the *Journal of Clinical and Translational Science*.[12] But in reality, a comprehensive biostatistical view of the entire research strategy is critical.

Research teams must finalize the SAP before data analysis can begin. The SAP details the primary, secondary and safety analyses, along with "possible data transformations, applied point and interval estimators, statistical tests, subgroup analyses and the consideration of interactions and covariates. Furthermore, the used data sets (for example intention to treat or per protocol), the handling of missing values and a possible adjustment for multiplicity should be described and discussed," Ciolino et al. note.

Biostatisticians apply statistical techniques to data collected during a clinical trial to draw conclusions from that data and identify trends. Therefore, Effat writes, it's critical that biostatisticians help determine which techniques are most appropriate for a given study and dataset.

"Clinical research reporting includes statistical methods and briefing of the method, data interpretations and visual representation as part of the collaborative process between biostatisticians and researchers," he notes.

Clinical research teams can also lean on biostatistics to help evaluate primary and secondary trial endpoints and ensure they are objectively measurable, are clearly and uniquely defined, and match the goals of the study, Zapf et al. say. Biostatisticians can play a key role in flagging potential problems with multiple or composite primary endpoints and surrogate variables. Other areas in which biostatistics play a key role during study design and planning include:

- Selecting blinding and randomization techniques to avoid bias;
- Specifying comparators or treatment arms and definition of how they are embedded in the study design, e.g., parallel or crossover; and
- Implementing procedures for data capture and processing.

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Biostatisticians also help the research team analyze objectives, data analysis methods and the overall study design, Effat notes. Credevo agrees, writing that biostatisticians' specific contributions during clinical trials typically include:

- Providing advice during protocol development and study design;
- Ensuring that enrolled patients are correctly randomized;
- Playing a key role in data management and monitoring; and
- Defining data analysis and creating tables and figures for the clinical study report.

Biostatisticians may also assist with CRF development and dataset specifications. Key duties include ensuring that data formatting is correct and selecting the data to be pooled, Credevo writes.

"The quality of medical research importantly depends, among other aspects, on a valid statistical planning of the study, analysis of the data and reporting of the results, which is usually guaranteed by a biostatistician," Zapf et al. say.

Biostatisticians can flag data management flaws

A data management plan is crucial for any clinical trial. When the research team is formulating this plan, biostatistician input helps identify potential flaws in data collection, according to Effat. Biostatisticians can uncover deficiencies, helping determine whether or not a treatment is safe and effective and the causes of particular diseases, he says.

Databases are critical to allow clinical researchers to record and propagate scientific information. The database must be more than just a repository of information, Gill et al. stress in *Perspectives in Clinical Research*; it must allow effective data management, which includes:

- Efficient data collection at a single point;
- Rapid data output in the desired format;
- User-friendly restricted access;
- A strong audit trail process;
- Authenticated data completion, integrity and quality; and
- Easy and efficient data archiving.

Having a cohesive, usable database can be challenging, as data used in clinical trials may come from different sources and may be structured, unstructured or semi-structured. This variation can pose challenges to consistent collection, storage and analysis.

Biostatistics play an important role in conducting tasks such as integrating electronic data capture and remote monitoring. Biostatisticians work with these tools to ensure secure and efficient data capture, high accuracy and streamlined data management, with the goal of faster analysis and improved data quality, according to ICON.

This includes use of third-party data sources and wearable devices that transmit patient data to clinical researchers automatically, the CRO adds. Biostatisticians are essential to ensure that data from diverse sources is compatible, adheres to all regulatory requirements and meets quality standards.

A variety of clinical data management tools are available` to help acquire, store, distribute and analyze the wide range of data used in clinical trials, Gill et al. note. They include:

- Cloud-based predictive analytics to finds patterns in clinical datasets;
- Natural language processing to turn unstructured data such as narrative clinical notes into structured data; and
- Secure cloud-based data storage that can be accessed and distributed easily from any location.

Data integrity is a critical consideration in clinical research, ICON emphasizes. Any question about the integrity and validity of data submitted from a clinical trial could endanger the approval of the investigative product. Biostatistics are vital to ensuring the accuracy and quality of all data collected from patients enrolled in a clinical trial. In tandem with data managers, biostatisticians develop data management plans designed to ensure that data collection, coding and storage is done in a standardized and scientifically rigorous manner.

This helps to ensure that trial data is complete, accurate and consistent, thus reducing the risk of errors, facilitating efficient analysis and providing regulatory assurance of the quality of the data submitted.

Biostatisticians generally adhere to Clinical Data Interchange Standards Consortium (CDISC) standards for data collection and analysis, ICON notes. This can help support data comparability and interoperability across studies. The FDA and other regulators generally prefer that data be submitted following these familiar standards, so their use can also enhance regulatory compliance.

They also apply data quality oversight methods that can help identify patterns of data issues that may not otherwise be apparent. This includes analyzing data from multiple sites, countries and patients to identify outliers and potential sources of bias.

"By detecting and addressing data issues early on, biostat-

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isticians contribute to the overall quality and integrity of the trial results," ICON writes.

Regulations, professional guidelines address trial design

Many pertinent regulations and professional guidelines specifically direct clinical researchers and sponsors to ensure that biostatisticians are involved from the earliest stages of study planning.

Regulators clearly expect to see biostatistics expertise applied to the design and the execution of any clinical trial. For example, the International Conference on Harmonisation (ICH) good clinical practice (GCP) guideline ICH E6 states explicitly that statistical expertise should be used throughout all stages of clinical research. Section 5.4.1 states, "The sponsor should utilize qualified individuals (e.g., biostatisticians, clinical pharmacologists and physicians), as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs [case report forms] and planning the analyses to analyzing and preparing interim and final clinical trial reports."[13]

Although the ICH GCP guideline does not have the force of law, the FDA and many international regulators have adopted the document as part of their own guidance documents, applying it under their enforcement authority.

Additionally, professional guidelines for biostatisticians in clinical research emphasize the early and ongoing participation throughout the design and implementation of a clinical trial. The Association for Clinical and Translational Science's special interest group on Biostatistics, Epidemiology and Research Design (BERD) has developed a guidance on the elements of research protocols that a biostatistician should consider in a review. The consensus guidance, which Coilino et al. describe in their paper, provides a checklist of those elements and discusses how each element should be reviewed. They are:

- **Objectives and hypotheses:** The objectives should be specific, measurable, achievable, relevant and time-bound. The hypothesis should follow from the objectives. Statistical tests of the hypothesis should be clear and match aims.
- **General approach:** The study design should match the objectives and hypothesis and address the research questions. Potential conclusions should have clear, evident limitations.
- **Population and sample:** The degree of generalizability should be obvious. Inclusion/exclusion criteria should be appropriate for the current state of knowledge. Screening and enrollment processes should minimize bias and avoid restricting diversity.
- **Measures and outcomes:** The choice of measurements, especially the response variable, must be justified and consistent with the objectives. The study visit schedule should be clear, all data standardized, ranges of outcomes clear and all algorithms justified. Measurement of important/standard explanatory variables must describe the sample or address confounding.
- **Treatment assignment:** Research teams must minimize biases using randomization and blinding. Control conditions must allow for comparability or minimization of confounding.
- **Data integrity and data management:** The data capture and management platform should be as described. Security and control of access to study data must be discussed. Data validation, error correction and query resolution processes must be included.
- **Statistical analysis plan:** The statistical approach must be consistent with the hypothesis and objectives. The dataset, unit of analysis and population (e.g., intention-to-treat set, per protocol set, full analysis set, etc.) must be clearly described. The plan should address key statistical assumptions, alternative approaches and methods to prevent and handle missing data.
- **Sample size justification:** Type I and II error rates should be present for all sample size calculations and corresponding statistical tests. Parameter assumptions must be clearly stated and justified (i.e., based on previous research). Statistical tests used in sample size calculations must match those in the SAP or include appropriate justification for differences.
- **Reporting and reproducibility:** There should be plans for sharing and archiving data. Version control procedures or other means of ensuring rigor, transparency and reproducibility are also important. There should be a plan to report results according to guidelines or law.

Elm used a courtroom analogy to explain how biostatistics work in clinical trials. In the U.S. court system, two competing hypotheses are presented: that the defendant is not guilty (the null hypothesis) and that the defendant is guilty (alternative). The jury makes its decision based on the available evidence, which equates to the data generated in a clinical trial. If the jury finds sufficient evidence, it will reject the null hypothesis

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and deem the defendant guilty. If the evidence is insufficient, the jury will accept the null hypothesis, meaning the defendant is innocent.

"In statistics, we always make one of two decisions. We either 'reject the null hypothesis' or we 'fail to reject the null hypothesis,'" Elm explains. This concept shapes how biostatistics are applied to evaluate endpoints, study population and other factors.

Biostatistics touches many areas

In the course of this work, biostatisticians end up working closely with several other professionals, including medical informatics and bioinformatics specialists and epidemiologists. Biostatisticians and bioinformatics experts often work closely together, especially when developing a data management plan and determining what computational tools could support it.

The Mayo Clinic, for example, emphasizes how biostatisticians interact with other research professionals before, during and after a clinical trial.[14] Biostatistics provide essential support for clinical research in myriad areas, including study design, data acquisition, data management, data analysis and data interpretation, according to the clinic.

At the Mayo Clinic, "the Division of Clinical Trials and Biostatistics collaborates with various research projects and provides a dedicated statistical team for a variety of studies," according to its website.

Biostatistics involves the development, implementation and use of specific statistical and mathematical methods to gain specific knowledge, Zapf et al. explain. Bioinformatics is concerned with the research, development and application of computer-based methods to answer medical research questions. It mainly focuses on models and algorithms for data at the molecular and cellular levels.

The two must work closely together, especially in the planning and design stages before a trial launches.

Clinical research organizations are increasingly engaging data collection and management specialists. This relatively new area of expertise often is used to describe and summarize all data-associated fields, Zapf et al. write. While biostatisticians and bioinformatics specialists may fall under the general umbrella title "data scientist," they are not data management generalists although they can have significant influence over the data management infrastructure.

Epidemiologists, concerned with the spread and course of diseases and their underlying factors in the public, also often work closely with biostatisticians. This is particularly true in research focused on the cause of disease and prevention of its spread.

Bioinformatics entwined with biostatistics

It is difficult to discuss biostatistics without referencing bioinformatics, which essentially refers to use of computational resources to evaluate biological data, Brandi Davis-Dusenbery, chief scientific officer of Seven Bridges Genomics, said in a Technology Networks interview.[15] Clinical bioinformatics is a developing science that incorporates clinical informatics, bioinformatics, medical informatics, information technology and mathematics to provide specific, targeted biological and medical information, Akanksha Suman et al. add.[16]

In this way, bioinformatics can be considered the information technology tools, including key algorithms used to analyze the specific dataset generated throughout the course of a clinical trial.

This is a relatively new tool in the development of diseases-specific biomarkers, mechanism-oriented understanding and individualized medicine, Suman et al. say. Bioinformatics is especially important in the arena of individualized healthcare.

Bioinformatics has increasingly been used in genomic and oncology research and in personalized medicine. It has great capacity to combine metabolomic and proteomic data with genomic data to paint a comprehensive pharmacokinetic profile of an investigational drug in the human body. One of the most famous examples of bioinformatics implementation is the Human Genome Project, which relied on informatics to analyze and sequence three billion chemical base pairs, Suman et al. note.

Integrating multiple data types in this way can help validate observations from a single data type, making this one of the most beneficial features of bioinformatic analysis, according to a Fios Genomics blog post.[17] In earlier stage research, bioinformatics helps assess toxicity, the post notes.

The oncology research arena, in particular, makes use of bioinformatics to identify precision treatment regimens for certain cancer patients, according to Davis-Dusenbery. For example, the UK Biobank and the Cancer Genome Atlas have enabled studies on disease pathology that have "spawned thousands of peer-reviewed publications enriching the collective knowledge of the scientific community," she told the publication. That work has led to breakthroughs in oncology, especially precision medicine for diagnosis and treatment of

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solid tumors.

This brings the discussion back to the topic of the ever-growing datasets seen in clinical research. Clinical trials generate massive amounts of data, all of which must be sifted through, organized and analyzed. Applying bioinformatics can help make that process more effective and efficient, according to Fios.

"Statistical programming is a critical aspect of biostatistics in clinical trials," ICON notes. "Biostatisticians use programming languages [such as] R or SAS to perform complex statistical analyses, generate tables and graphs, and visualize the study results. They ensure that the programming code is well-documented, reproducible and adheres to industry best practices."

For example, bioinformatic analysis is invaluable to help assess efficacy of an investigational treatment. By swiftly sifting through large databases of diverse information, bioinformatics can distinguish biomarkers that predict treatment efficacy and compare a novel treatment to the current standard of care. This information is invaluable in determining appropriate endpoints and the right metrics to determine whether they have been met.

Bioinformatics can also support biostatisticians in identifying groups of potential clinical trial participants. This goes beyond merely identifying those with a particular disease or condition, Fios says. For example, bioinformatics can help identify individuals who do or do not express certain signature genes or gene mutations that may affect how they respond to an investigational treatment. This can be important information when developing inclusion/exclusion criteria, as it can more clearly identify both patient groups that are likely to benefit from the novel treatment and those in which it would be contraindicated.

The right bioinformatics can also enhance the SAP. Careful choice of algorithms and other tools is crucial to guarantee the validity of statistical software, according to Zapf et al. Bioinformatics experts can help to ensure that such tools are the right pick for a study.

Data diversity, standards challenge bioinformatics

The bioinformatics field faces some challenges, according to Davis-Dusenbery. One is a lack of diversity and democratization of data.

"Most biobank and population-scale datasets tend to be monochromatic, lacking in representation of various racial, ethnic and socioeconomic profiles," she told *Technology Networks*. "While some institutions are taking steps to address the lack of diversity, the field is still developing the methodology to generate and utilize insights available through the analysis of diverse genomes."

Another major challenge is a lack of broadly accepted standards for indexing and formatting large and disparate datasets, she says. Data used in bioinformatic analysis is drawn from a variety of sources that can differ greatly in both content and format. The industry needs greater variable harmonization and better dataset interoperability, in general.

Nonetheless, bioinformatics has become a critical part of clinical research, alongside its sister discipline biostatistics. Applying the right software tools and the right statistical analysis techniques in tandem will help research sites better manage data points addressing multiple endpoints and coming from a variety of sources. And this leads to greater assurance that the right data is being collected to address the right questions, and that data quality and integrity are protected throughout the course of the clinical trial.

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Evidence-based research

1. Which of the following best defines evidence-based research?
   a. The use of prior research to inform a new study.
   b. The use of prior research to justify a new study regardless of its quality.
   c. The use of prior research to support a researcher's own agenda.
   d. None of the above.

2. What is the primary purpose of conducting systematic reviews to support evidence-based research?
   a. To identify gaps in current research.
   b. To reduce research waste and redundancy.
   c. To improve the quality of research studies.
   d. To ensure all research studies are published.

3. How many clinical researchers use systematic reviews to justify their research questions and study designs?
   a. Fewer than 25 percent.
   b. Fewer than 50 percent.
   c. Up to 75 percent.
   d. Up to 100 percent.

4. How do systematic reviews contribute to improving research quality?
   a. They help identify errors in existing literature and correct them.
   b. They help ensure research studies will contribute new information.
   c. They support well-known research authors.
   d. They confirm well-known study outcomes.

5. Which of the following is an aim of the Evidence-Based Research Network (EBRN)?
   a. Ensuring all new studies include a systematic review.
   b. Ensuring that all new research is justified.
   c. More efficient production of systematic reviews.
   d. All of the above.

6. Which of the following best describes a way to diminish waste and redundancy in clinical trials?
   a. Hiring additional onsite staff to handle more clinical trials.
   b. Requiring a plan for systematic review in funding applications.
   c. Researching the impact of evidence-based research on trials.
   d. Creating an ad campaign to promote evidence-based research.

7. According to Lund and his coauthors, which of the following is a characteristic of a systematic and transparent review?
   a. It focuses on all studies from well-known authors.
   b. It focuses on all studies that match the inclusion criteria.
   c. It focuses on all studies from obscure organizations.
   d. It focuses on all studies published by the lead researcher.

8. What is the term used to denote clinical studies that take the requirements of patients and practitioners into account in meaningful ways?
   a. Selective-led research.
   b. Needs-led research.
   c. Patient-centric research.
   d. Requirement-based research.

9. Which of the following is a model that seeks to connect evidence-based practice, evidence-based research and public engagement?
   a. Cumulative enterprise model.
   b. Bridge-building model.
   c. Transparent review model.
   d. Selective citation model.

10. According to Ormstad et al., why has priority-setting for clinical research been exclusively the domain of researchers and their funding bodies?
    a. Lack of clinician and patient interest.
    b. Lack of focus on high-impact work.
    c. Inadequate input from end users.
    d. Inadequate public funding.

Biostatistics and Bioinformatics

11. What is the primary role of biostatistics in clinical trials?
- a. Managing research sites.
- b. Ensuring data integrity and quality.
- c. Developing investigational treatments.
- d. Conducting patient enrollment.

12. True or false: The primary role of bioinformatics in clinical trials is designing, conducting, analyzing and interpreting data generated during the trial.
- a. True.
- b. False.

13. What distinguishes bioinformatics from biostatistics?
- a. Bioinformatics deals with a larger volume of data.
- b. Biostatistics focuses on computational algorithms.
- c. Bioinformatics is concerned with designing clinical trials.
- d. Biostatistics analyzes data at the molecular level.

14. What is the primary goal of biostatistics in clinical trials during the study planning period?
- a. Finalizing the statistical analysis plan (SAP).
- b. Calculating the right sample size.
- c. Ensuring data collection protocols.
- d. Developing investigational treatments.

15. Why is bioinformatics considered especially valuable in oncology clinical research?
- a. It analyzes clinical datasets.
- b. It determines the study population size.
- c. It identifies precision treatment regimens.
- d. It finalizes the statistical analysis plan.

16. What is the role of biostatisticians in data management plans?
- a. Ensuring efficient data capture.
- b. Ensuring secure data capture.
- c. Ensuring accurate data capture.
- d. All of the above.

17. Which organization's guideline explicitly states that statistical expertise should be used throughout all stages of clinical research?
- a. The World Health Organization.
- b. The International Conference on Harmonization (ICH)
- c. The Food and Drug Administration.
- d. The Centers for Disease Control and Prevention.

18. What is the primary responsibility of biostatisticians during the study design and planning phase?
- a. Selecting the ideal sample size.
- b. Analyzing interim data.
- c. Developing investigational treatments.
- d. Finalizing the statistical analysis plan.

19. How do biostatisticians contribute to the results in the study report and publications?
- a. They design clinical trials.
- b. They analyze interim data.
- c. They write the statistical section of the clinical study.
- d. They develop investigational treatments.

20. Which of the following is crucial for data comparability and interoperability across studies in clinical research?
- a. Using software that automatically captures electronic data.
- b. Adhering to clinical data interchange standards.
- c. Using visualization techniques.
- d. Monitoring for interim data errors.