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Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

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Changed for the Better: A Brave New World for Researchers and Patients in 2021

Clinical Researcher™

Association of Clinical Research Professionals

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EXECUTIVE DIRECTOR'S MESSAGE

Trying Times Bring Changes for the Better

Jim Kremidas

We've just wrapped up the first track of our ACRP 2021 Virtual Conference, and I couldn't be more excited about how it went. I hope you got a chance to attend. If you did, you heard some great sessions on topics ranging from decentralized trials to how the clinical research landscape has forever been changed due to COVID-19.

In these times of remote work, I think the virtual conference has helped to fill a void. Throughout the event, I was so glad to see how many attendees were asking questions of speakers, then chatting amongst themselves before and after sessions, and then visiting our virtual expo hall to talk with service providers and other experts.

No, it's not quite the same as meeting face to face in Seattle or Nashville, but many of you told me how good it felt to be able to catch up with colleagues around the country—even if it was on a screen!

The theme of this month's *Clinical Researcher* is "Changed for the Better," and how to improve upon our current circumstances in the clinical trials arena came up often in terms of budgeting and billing during our virtual conference. I don't have to tell you these have been challenging times for many, especially for sites with tight cash flow and precarious trials either on hold or facing other kinds of uncertainty, but changes being made to processes, procedures, and policies in response to such stresses are making life better for researchers and patients.

It occurred to me while watching one of the conference sessions about budgeting for a clinical trial that, at its best, ACRP can be a safe place for you to come with concerns, questions, and worries about the future of medical research. We aren't soothsayers, but we are able to gather many of the most knowledgeable thought leaders across the entire trial spectrum. Together, our shared experiences can further raise the bar for clinical trial quality.

We have a number of webinars and other events lined up in the calendar already, with more to come. I invite you to join us online in May, when we continue the virtual conference with a focus on operational efficiencies. In September, we'll regroup to look at new regulations affecting the clinical research enterprise.

The clinical trial workforce performed heroically in 2020, and the world is grateful for the work you've done developing vaccines in record time. As we move into a new year, I hope ACRP can continue to support your valiant efforts.

Jim Kremidas (jkremidas@acrpnet.org) is Executive Director of ACRP.

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CHAIR'S MESSAGE

Facilitating Networking Through Technology

Erika Stevens, MA

Does technology facilitate networking? While more video conferencing platforms flood the market to enable interactive meeting collaboration, omitted is the camaraderie gained through non-digital interaction.

Technology-enabled business meetings may close the distance gap and reduce travel inefficiencies, but few address the social interface gained through physical proximity. Recall from your memory: mingling, meeting new contacts, seeing old colleagues and friends, "meet and greets," and happy hours. Less than one year ago, these forms of social interaction were everyday occurrences. Missing today is the ability to shake hands, split an appetizer, or embrace a longtime friend.

Leveraging technology innovation for presentations, on-screen chats, exchange of ideas, and decision making facilitates many former face-to-face business meeting operations. None of these capabilities provides an adequate replacement for tangible connectivity gained through interaction. The subtle nuances garnered through gestures and facial expressions are often unseen in virtual forums. In the absence of in-person meetings, restricted social gatherings, and fear of human contact, we are forced to plod along on screen.

While imperfect, virtual interaction allows increased frequency for sharing ideas and information. We continue to develop agility with multiple applications and improve social interfaces. Some unnoticed, nonverbal cues providing connotation clarity remain vague, but we evolve and adapt.

As the world pandemic brings the clinical research industry into public view, it further bolsters the value of membership in the Association of Clinical Research Professionals (ACRP). At the same time, sustained infection rates cause notable concern and impede networking. For example, on January 15, ACRP received notice of cancellation of our planned 2021 conference from the city of Toronto due to COVID-related concerns.

Disappointingly, another year will pass where fellow ACRP members are not able to meet in person. Like my ACRP Association Board of Trustees colleagues, I will miss seeing you in person in Toronto this spring. Instead, we look forward to gathering virtually and facilitating dynamic networking opportunities. Your valiant efforts support the therapies to combat illnesses plaguing society. Thank you for your membership with ACRP.

I wish you all the best jusqu'a la prochaine fois (until the next time).

Erika Stevens, MA, has more than 20 years' experience in the research industry, is the 2021 Chair of the Association Board of Trustees for ACRP, and leads Transformation Advisory Solutions for Recherche Transformation Rapide. She advises life sciences companies, health systems, academic medical centers, foundations, hospitals, and contract research organizations in process improvement initiatives for quality and efficiency in operations, cross-functional relationships, administration, manufacturing, and compliance. Her earlier volunteer duties with ACRP include service as Chair of the Editorial Advisory Board, a member of the Conference Planning Committee, and President of the New York Metropolitan Chapter.

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PEER REVIEWED

The Journey from Biologic to Biosimilar—A Clinical Perspective

Wasi Akhtar, BPharm, MBA

Biosimilars, even though they are newer versions of existing, trade-name biological products whose patents have expired and share identical amino acid sequences with those earlier products, are not identical to the reference product. Biosimilars do not utilize the same living cell lines, production processes, or raw materials[1] as the innovator drugs (the reference originator biologics).

As novel drug development expands in the 21st century, biologics are leading the way, yet they correspond to the costliest of treatments. It is anticipated that using biosimilars will lead to an estimated $54 billion reduction in direct spending on biologic drugs from 2017 to 2026 (all monetary statistics in this article are in U.S. dollars).[2]

A **Reference** product is a single biological product, already approved by the FDA, to which a proposed biosimilar product is compared.

A **Biosimilar** is a biological product that is highly similar and has no clinically meaningful differences from an existing FDA- approved reference product.

An **Interchangeable** product is a biosimilar product that can be substituted for the reference product without the intervention of the prescribing healthcare provider.

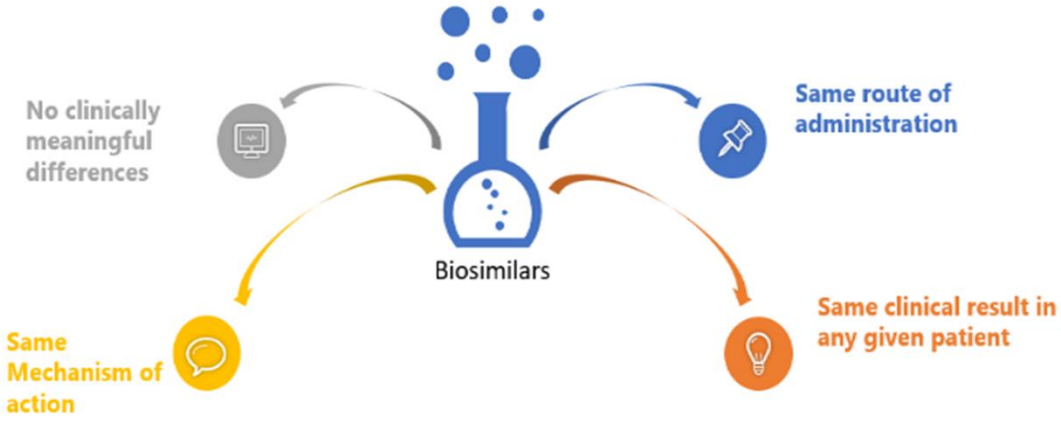
Source:
https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

At present, the total number of biosimilars approved by the U.S. Food and Drug Administration (FDA) is 28, with Hulio being the most recent approval.[3] The FDA's support of biosimilars has instilled confidence among pharmaceutical companies to pursue their development as a positive trend for both consumer needs and corporate viability.

[1] Declerck P, Farouk-Rezk M, Rudd P. 2015. Biosimilarity Versus Manufacturing Change: Two Distinct Concepts. *Pharmaceutical Research* 33. 10.1007/s11095-015-1790-3.
[2] Mulcahy AW, Hlavka JP, Case SR. 2018. Biosimilar Cost Savings in the United States: Initial Experience and Future Potential. *Rand Health Q* 7(4):3. PMID: 30083415; PMCID: PMC6075809.
[3] https://www.fda.gov/drugs/biosimilars/biosimilar-product-information

This article provides insight into the guidelines issued by the FDA regarding considerations related to biosimilars development. Important considerations include the role of data analysis and a focus on such key concepts as the totality of evidence, data requirements, immunogenicity, and interchangeability.

Key Attributes of Biosimilars as Related to Biologics



Background

Biologics (also known as genetically engineered or biotech products) are a class of medications produced from living cells using recombinant techniques. This class of medication is comprised of large molecules with a complex structure that includes a primary amino acid sequence, higher order secondary and tertiary structures, and various post-translational modifications.

A biosimilar is a "highly similar" biological product to one that has been previously approved by the FDA, and shall have no clinically meaningful differences in terms of safety, efficacy, and purity; however, there can be few minor changes in terms of active ingredients. The biosimilar product should have an identical route of administration, strength, and dosage form as the earlier product and, like all FDA-approved products, must comply with Good Manufacturing Practices demonstrating drug quality.[4]

[4] https://fas.org/sgp/crs/misc/R44620.pdf

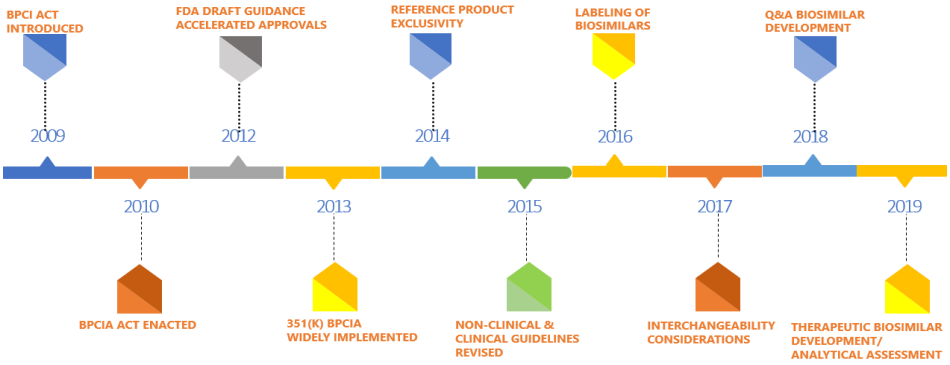
Definitions from the FDA, European Medicines Agency, and World Health Organization[5]

US FDA	EMA	WHO
A biosimilar product is a biological product that is approved based on a showing that is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products	A similar biological or biosimilar medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use	A similar biotherapeutic product is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licence reference biotherapeutic product

While Europe revolutionized the development and medicinal applications of early biologic products such as vaccines and antitoxins, the United States has been leading the innovations in biotechnology and biologic therapies in the 21st century.

The Patient Protection and Affordable Care Act of 2010 allows the approval of biosimilars in the U.S. and allows certain clinical and nonclinical requirements for drug approval to be waived if regarded as unnecessary by the FDA.[6]

The Evolution of Biosimilars in the U.S.[7]



[5] https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products (FDA)
https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview (EMA)
https://www.who.int/bulletin/volumes/96/4/17-206284/en/ (WHO)

[6] https://www.fda.gov/drugs/guidance-compliance-regulatory-information/implementation-biologics-price-competition-and-innovation-act-2009

[7] http://gabionline.net/Reports/The-evolution-of-biosimilars-in-the-US

Methods

This clinical perspective overview was performed by analyzing the FDA's regulatory policies, guidance documents, and related information for the biosimilar pathway, as well as by reviewing related literature and opinions from publicly available websites.

Trends and the Territory for Biosimilars

According to Grand View Research, Inc., the biosimilar market is expected to grow at a CAGR of 34.2% and attain a global value of $61.47 billion by 2025. The market for biosimilars in the U.S. is growing at a steady pace owing to high drug costs and production timelines.[8]

Unlike the case for generic drugs, for biosimilars there is an abbreviated pathway for approval that must validate that they are highly similar to the reference biologic and that there are no meaningful differences from the clinical perspective. There is a concept of interchangeability, by which the FDA means a product (with an interchangeable designation) can be replaced with the reference biologic without the intervention of the prescriber.[9] The "high similarity" between the proposed biosimilar and biologic (reference product) must be demonstrated.[10]

The production of biosimilars is a complex, multi-step procedure; at each stage, such factors as the production cell line, culture conditions, and formulation may alter the final product through post-translational modifications. Since biologics and biosimilars are created in living cells, they cannot be chemically synthesized like generic drugs.

An Abbreviated Biologics License Application (aBLA) to FDA for the proposed biosimilar should include information demonstrating biosimilarity, particularly the data derived from the analytical studies for clearly proving and demonstrating "high similarity" to the reference biologic.[11]

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[8] https://www.grandviewresearch.com/press-release/global-biosimilars-market

[9] https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

[10] https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

[11] https://www.fda.gov/media/119258/download

FDA Approval of Biosimilars

The Biologics Price Competition and Innovation Act (BPCIA) of 2010, through the abridged approval pathway for biosimilars, allows approvals in fewer steps as compared to the reference product. However, this certainly does not mean that lower standards have been adopted by the FDA for the abbreviated pathway, as the producers of biosimilars should furnish extensive data packages that meet the stringent standards determined by the agency.

The assessment of biosimilars is performed on a case-dependent basis, and each application's data requirements will vary accordingly. Typically, the FDA considers the following types of data while assessing a biosimilar:

Analytical Studies—To illustrate the molecular profile of the biosimilar in a manner showing high similarity to the reference product, both from structural and functional perspectives.

Animal Studies—To evaluate toxicity of the biosimilar.

Clinical Pharmacology Studies—To give proof of evidence in terms of safety, quality, and efficacy of the biosimilar (may include pharmacokinetic (PK) and pharmacodynamic (PD) assessments).

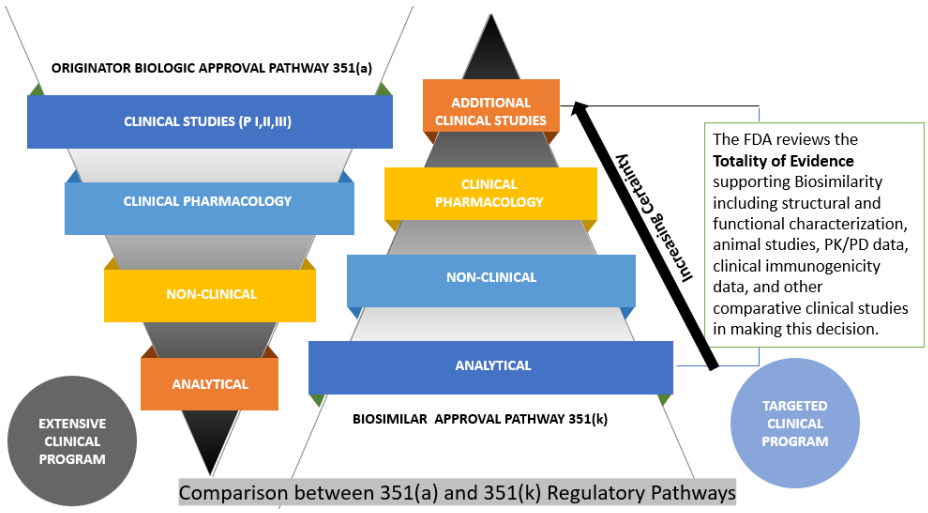
Additional Clinical Studies of Biosimilarity—The objective of a biosimilar development procedure is to validate high similarity between the biosimilar and reference product, rather than separately establishing the safety and efficacy of the proposed product.

Totality of Evidence

The FDA has a very robust approach toward the evaluation of biosimilarity called "Totality of Evidence," which is aimed at comparative testing and approvals (depicted below). The agency advises the developers of biosimilar candidates to take a multi-step approach and, at each step, to compare the candidate to the biologic (reference product), evaluate it in terms of where there may be residual uncertainty, and perform studies aimed at mitigating those uncertainties. Each step in the biosimilar approval pathway should decrease residual uncertainties from the previous stage.[12]

[12] Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. https://www.fda.gov/media/82647/download

Comparison Between Innovator and Biosimilar Regulatory Pathways[13]



Data Requirements for Development of Biosimilars

A biosimilar application should demonstrate biosimilarity by providing highly similar characteristics to the reference product; rely on the creation of design space based on analysis of the reference product and the sequential multiple testing of the biosimilar. The major development and application fundamentals are summarized below:

- Design controls, validation, and verification studies
- Biosimilar development through quality by design approach
- Analytical similarity through statistical data
- Clinical aspects
- FDA Guidance on Biosimilar Labeling

Demonstration of Biosimilarity from Clinical Pharmacology Data

This typically involves three key concepts—exposure and response assessment, evaluation of residual uncertainty, and assumptions about analytical quality and similarity.

[13]https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval

While determining the safety, efficacy, and purity of any biological product, it is essential to evaluate the "exposure and response" along with a thorough assessment to ascertain any possible clinically meaningful difference between two products. The response is a precise measure of the pharmacological aspects in relation to effectiveness and adverse reactions.[14]

Immunogenicity and Safety Assay

This assay describes the generation of the immune response within the body to a biotherapeutic that may result in immune-mediated toxicity and/or a lack of effectiveness. Biologic drug treatments introduce a foreign substance, in response to which anti-drug antibodies (ADAs) may form. Due to this, there can be serious safety and efficacy implications for biosimilar drug programs; for example, ADAs may block the functionality of the biosimilar, greatly alter the PK of the biosimilar in a biologic system, or even cause acute and long-term health consequences. In such cases, it might not be suitable for additional studies to be conducted, largely depending on the extent of such potential safety and efficacy concerns.[15]

At least 36 publications have presented primary evidence explaining the effectiveness of biosimilars that followed on from major biologics with proteins 200 amino acids in length or greater (including etanercept, adalimumab, infliximab, and rituximab). ADAs were tested in 24 experiments considering larger biosimilars, and seven provided details on neutralizing antibodies (NABs).

Among the smaller biosimilars, 13 studies measured ADAs and four presented NABs (erythropoietin, filgrastim, human growth hormone). In all the studies documenting immunogenicity results, ADA and NAB levels were found to be comparable across all disease indications and treatment groups at baseline and at the end of the study, the authors add.[16]

[14] https://www.fda.gov/media/82647/download
[15] Krishna M, Nadler SG. 2016. Immunogenicity to Biotherapeutics—The Role of Anti-drug Immune Complexes. *Front Immunol* 7:21. doi:10.3389/fimmu.2016.00021
[16]https://www.centerforbiosimilars.com/view/systematic-literature-review-shows-low-risk-of-safety-concerns-or-loss-of-efficacy-after-switching-to-a-biosimilar

Trial Designs for Developing Data Regarding Biosimilars

A crossover design is acceptable, if possible, for PD studies using products with a short half-life (e.g., less than five days), a rapid PD response, and a low incidence of immunogenicity. However, this type of clinical trial is most sensitive to PK assessment of similarity.

A parallel design would typically be needed for products with a longer half-life (e.g., more than five days) or for which recurring exposures may lead to an increased immune response, thereby effecting the PK/PD assessments to derive similarity. Scientific rationale for the choice of the research dose (e.g., one or several doses) and route of administration should be provided by the sponsors.

Population Type to Use for Study

PK/PD studies to demonstrate similarity can be performed with healthy volunteers, as this practice is often considered to deliver more sensitivity in the results and as being likely to produce less variability in PK values as compared to patients with underlying diseases and associated medications. However, if safety and other considerations prohibit the involvement of healthy volunteers, the clinical pharmacology studies can be conducted in patients.[17]

Dose

The appropriate dose that can provide clinically significant and understandable data should be chosen. For example, in scenarios where the studies are performed in a patient population, the standard dose for the reference biologic product might be the suitable choice, as this might best determine the pharmacological effects in a clinical setting.

Route of Administration

When conducting in-human PK and PD studies, the route of administration for the proposed biosimilar product should ideally be the same as for the reference product.[18]

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[17] https://www.fda.gov/files/drugs/published/Bioavailability-and-Bioequivalence-Studies-Submitted-in-NDAs-or-INDs-%E2%80%94-General-Considerations.pdf

[18] https://www.fda.gov/media/88622/download

PK Measurement

In the case of a single-dose study, the total exposure must be calculated as the area under the biological product concentration-time curve from time zero to time infinity; however, in the case of multiple-dose studies, the measurement of total exposure must be the area under the concentration-time profile from time zero to time tau over a dosing interval at steady-state.[19]

Extrapolation of Evidence on Effectiveness and Safety to Other Indications

The safety and efficacy of biologics should be determined in clinical trials in order to gain approval for each clinical use or indication sought. Extrapolation is the approval of a proposed biosimilar product in one or more additional indications for which the reference biologic is licensed, whereas the biosimilar has not been studied in clinical trials.

There are some items that the FDA says should be scientifically justified when considering extrapolation of signs and symptoms. The first is that the mechanism of action in the state of use—including the target/receptor for each biosimilar activity/function, binding, dose/concentration reaction, molecular signal pattern for target receptor involvement, and relationship between the biosimilar structure and target/receptor interactions and target/receptor position and expression—should be the same.

Extrapolation is based on all the evidence available in the biosimilar application, previous protection and efficacy results accepted by the FDA for other licensed reference product indications, and the understanding and evaluation of different scientific factors for each reference product.

Indication extrapolation reduces or removes the need for some indications of interest to already have been approved for the reference product when studying the potential biosimilar in clinical trials. This concept is crucial to achieving the goals of abbreviated approval pathways for

[19]https://www.fda.gov/files/drugs/published/Bioequivalence-Studies-With-Pharmacokinetic-Endpoints-for-Drugs-Submitted-Under-an-Abbreviated-New-Drug-Application.pdf

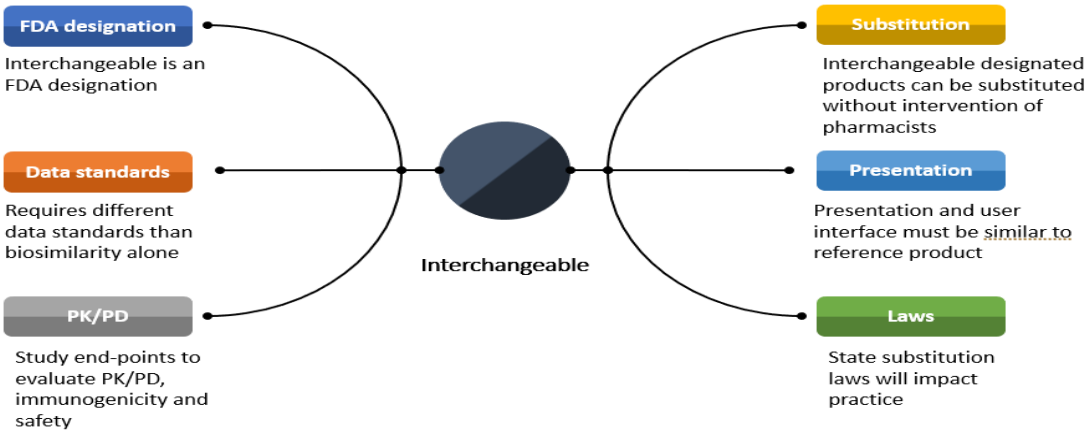
biosimilars at a substantially lower cost. Some of the characteristics that may be considered for extrapolation are summarized below:

- Mechanism of action in each condition
  - Binding and molecular signaling
  - Location and acceptance of target/receptor
- PK and biodistribution
  - PD methods may also provide important mechanism of action information
- Expected toxicities
  - Differences may exist in each condition of use and patient population

Interchangeability

Interchangeability is a subset of biosimilar products defined within the statute, which basically means the biosimilar product can be substituted for the reference biologic product without the intervention of the prescriber. It is expected that the biosimilar will provide the same clinical result as the reference product in any given patient. Additionally, if it is a multi-use product (products that are administered more than once), switching or alternating between the proposed interchangeable and the reference biologic product should not increase the risk of safety or diminished efficacy compared with using the reference biologic product multiple times.[20]

Key Attributes of an Interchangeable



[20] https://www.fda.gov/media/82647/download

Conclusion

The FDA has implemented legal frameworks for authorizing the development and marketing of biosimilar medicinal products. Based on the FDA guidance, comparative clinical safety and efficacy data will be necessary if there are residual uncertainties about the biosimilarity of the two products being compared.

Biosimilar product development follows a stepwise approach for determining the similarity of a reference biologic and proposed biosimilar. Clinical pharmacological studies play a crucial role in demonstrating biosimilarity and involve microbial and chemical analyses, *in vitro* biological patency assay, *in vivo* toxicological studies, and human clinical studies.

To determine biosimilarity of the proposed product to a reference biologic, the clinical pharmacology data are extremely important. PK and PD data are critical to support assertions of the clinical similarity between the biosimilar product and the reference product. An exposure-response assessment can significantly abbreviate the clinical development pathway of a biosimilar. PK/PD studies may replace a Phase III therapeutic equivalence study for biosimilars.

Resources

Questions and Answers on Biosimilar Development and the BPCI Act Guidance for Industry. https://www.fda.gov/media/119258/download

Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed. https://www.fda.gov/media/134932/download

Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry. https://www.fda.gov/media/125484/download

Hunter SA, Cochran JR. 2016. Cell-Binding Assays for Determining the Affinity of Protein-Protein Interactions: Technologies and Considerations. *Methods Enzymol* 580:21–44. doi: 10.1016/bs.mie.2016.05.002

Alten R, Cronstein BN. 2015. Clinical Trial Development for Biosimilars. *Semin Arthritis Rheum* 44(6 Suppl):S2–8. doi:10.1016/j.semarthrit.2015.04.002. https://pubmed.ncbi.nlm.nih.gov/26058550/

Reinisch W, Smolen J. 2015. Biosimilar Safety Factors in Clinical Practice. *Semin Arthritis Rheum* 44(6 Suppl):S9–15. doi:10.1016/j.semarthrit.2015.04.005. https://pubmed.ncbi.nlm.nih.gov/26058551/

Isaacs J, Gonçalves J, Strohal R, Castañeda-Hernández G, Azevedo V, Dörner T, McInnes I. The Biosimilar Approval Process: How Different is it? https://considerations.bmj.com/content/1/1/3

Heinemann L, Khatami H, McKinnon R, Home P. 2015. An Overview of Current Regulatory Requirements for Approval of Biosimilar Insulins. *Diabetes Technol Ther* 17(7):510–26 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504437/

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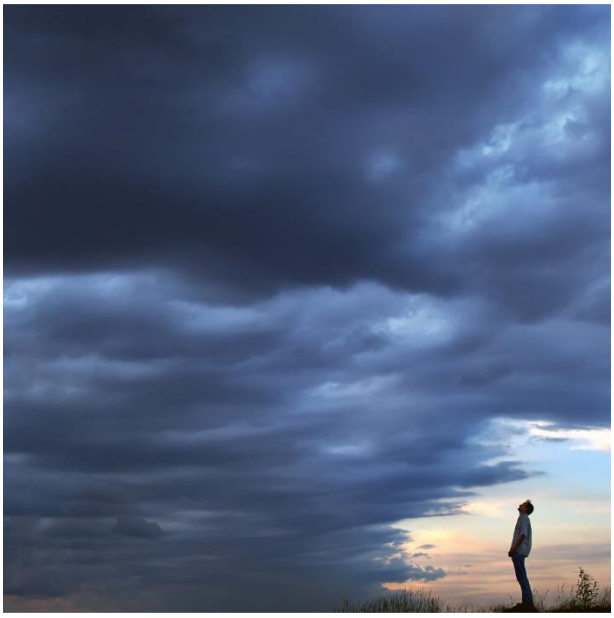
PEER REVIEWED

5 Lessons for Clinical Researchers from Education's Transition to Remote Learning

Mary Costello



Change is never easy, and this past year has presented the world with some seemingly insurmountable challenges—certainly among the biggest faced by any generation living today. As an industry rooted in continuous learning and experimentation with a mission to find new solutions, the clinical research enterprise continues to struggle with how to uphold that mission in a world that needs to limit in-person interactions. The very nature of the work has traditionally demanded the kind of in-person contact that now needs to be limited.

As the COVID-19 virus reached pandemic levels in early 2020, educational institutions around the world were upended almost overnight. Schools and universities closed, and educators had to redesign entire methodologies in ways that suited very diverse populations. Likewise, most clinical trials came to a screeching halt. Clinical trials stakeholders quickly realized that this was more than a brief setback; not only did they need to formulate a strategy for the continuation of research through virtual and hybrid studies, but the onus of developing treatments and vaccines for COVID-19 rested squarely on their shoulders.

The re-engineering of education continues to evolve as the pandemic lingers, but clinical research can benefit from what educators have already accomplished. What follows are five key lessons learned from educators and students, translated to the clinical research environment for consideration when developing training and trial conduct strategies going forward.

Change Management—Start Where the Patient Is

The traditional urge for a strong educational focus on study components when training clinical researchers has been compounded by the need to upskill staff and patients in technology. Significant changes such as a wholesale switch to decentralized trials require a sturdy foundation. Short-circuiting the thoughts, feelings, and downstream effects of everyone involved will not result in a successful transition. It is vital for both trainers and their "students" to acknowledge the potential for confusion, fear, and learning curve difficulties to be experienced by research team members and patients faced with learning about and using new trial-related technologies and procedures.

According to J. A. Miller, PhD, "Being open to the current crisis-driven educational opportunity is a call to action. The reputation and integrity of your institution—and you!—depends upon your offering engaging online classes."{1} The same holds true for clinical research, as the need to embrace virtual and hybrid trials is not temporary.

Staff, patients, and physicians all have concerns and questions that are unique to their roles. Beyond that, issues such as comfort with, and access to, internet services and smartphones vary by age, culture, and other socioeconomic factors. Beyond devices and internet speed, multiple platforms, logins, and lack of integration further complicate the learning curve. For research processes, study teams and patients are experiencing these same challenges. Utilizing a decentralized trial platform with a single sign-on for all research tasks will mitigate such challenges for all stakeholders.

The next step is to develop a thorough formative assessment to understand how well participants are engaging with the new technologies and procedures inherent in virtual and hybrid trials. This will guide further process design and resource allocations.{2} DePaul University Associate Professor of Political Science Molly Andolina, PhD, explains that a roadmap of transition for a

program from in-person to hybrid or remote is imperative. Both staff and patients should have checklists. She says, “Turning on a dime, as we had to do [at DePaul in early 2020], just did not work well.”

The plan for general implementation should include a thorough training process for staff and patients. Training vehicles should comprise a mix of written documents, live web meetings, interactive online modules, and short videos. Ideally, videos for younger users should last two minutes, as their attention span drops off significantly after that.{3}

To address the mental and emotional factors, consider incorporating a role play for staff that reflects the new day-to-day workflow. To build empathy for the patient experience, staff should also participate in role play of patients, particularly since they will be a source of tech support for patients. Establishing a “super user” at each site will help alleviate fears of what might go wrong and who will provide support.

Further, it is essential that training goes beyond features and functions to incorporate the “whys” for staff and patients. With any new process, understanding the why and how each person benefits helps to ensure success. When creating messaging to staff and patients about the new options, reinforce that they represent opportunities to ease burdens and improve workflows for everyone. The message should address security and privacy of information and reflect patients’ cultural sensitivities. For example, in some countries, patients will not want private health information, such as images of a medication, stored on their mobile device. Communicate with study teams, investigators, and patients that there will be options for how to participate in a study.

“I think that too often the focus is on what’s lost and not on what’s potentially gained” regarding remote instruction, said Chris Dede, a professor at the Harvard Graduate School of Education who has studied the use of educational technology in schools.{4} If we take this perspective when considering virtual and hybrid trials, adoption will be easier.

Process Design—The End is the Beginning

Consider the desired outcomes for the proposed research team and/or patient training and technology usages first, then back into the process design. Strip down expectations to be sure each step is truly necessary to achieve the outcome. Like lean methodology, if a component does not have value, it has no place in the value chain. The influence of site perspective on trial design is also imperative.

Carefully evaluate which components of each study can be conducted virtually. For example, with remote monitoring devices, sites can accurately collect vitals such as weight and blood pressure without an in-person visit. Structures need to be in place for responding to data collected through the technology, and this may require new decision support processes. Map out the best options, including those that are already part of the infrastructure. An example of a progressive implementation of virtual solutions is illustrated below.

Solutions	Lightweight Accelerated Virtualization	Accelerated Virtualization	Accelerated eCOA Virtualization	Full Scope Decentralized Trial
eConsent	●	●	●	●
Televisits	●	●	●	●
Surveys (25 questions or less)		●	●	●
Daily Diaries		●	●	●
Screening			●	●
eCOAs (scales & instruments)			●	●
Remote Physiologic Monitoring				●
Medication Adherence				●
Medication Distribution				●
Home Nursing and Labs				●
Multi-geography	●	●	●	●
Multi-Language	●	●	●	●
Estimated Deployment Timeline	2-4 weeks	3-5 weeks	6+ weeks plus eCOA scale timeline	Varies based on study

When choosing a decentralized clinical trial platform, make sure it integrates with wearables and patient-collected data. Single sign-on is also paramount to reduce complexity for staff and patients alike. College students have reported missing assignments, surprise quizzes, or other confusion because information for a single course might be housed across six different platforms. If the aim is to put the patient at the center, digitization must be seamless.

Remote and hybrid learning have created the potential for new teaching models. Some schools have enlisted specific virtual learning teams to develop and provide virtual instruction for remote students, while continuing to utilize existing teachers for classrooms with students attending in-person. For remote instruction, “learning navigators” can be leveraged to help students, teachers, and families use technology effectively.{5} The lesson is to use this opportunity during process redesign to evaluate staffing patterns and optimize the skill sets within the research team.

Once processes are redesigned, update operating procedures, job descriptions, and performance criteria to reflect technology proficiency and new workflows. Additionally, many sites have found that virtual and hybrid trials offer flexibility for staff to work remotely on occasion, particularly when kids are at home participating in distance learning. Designing standards that align with security and privacy regulations may seem daunting, but many have found that the added flexibility helps retain valuable team members.

As the clinical research enterprise moves forward with new processes and uses of technology, feedback must guide its progress. Using short surveys, input can be gathered from patients *and* staff at regular intervals; more importantly, responses to their feedback with meaningful changes will continue the cycle of improvement.

Contingency Plans—Preparation is Half the Battle

With any new process or technology, there will be hurdles, so it is important to create contingency plans for staff and patients; if they are prepared for the occasional glitch, they are less likely to experience distress when it occurs, and therefore more likely to stay engaged. Keeping FAQs updated and making short videos available on how to handle common issues like pop-up blockers, browser type differences, and time-out errors greatly reduce time that staff spend providing tech support.{1} Troubleshooting tips can be created in partnership with the site’s information technology group or technology vendor and customized by staff through training and role play exercises.

Creativity and Flexibility—One Size Does Not Fit All

Both education and research are rooted in methodical rigor. Study teams and research participants are conditioned—rewarded even—for rigor. However, the need for creativity and flexibility must be recognized. Factors that contribute to differentiated needs in online environments include technical skills, site capabilities, participant disabilities, economic hardships, or unstable home environments.{5}

“Remote education can’t be a simple replication of the in-person classroom interaction,” says Professor Andolina, and the same is true of clinical research. Patients need the ability to choose which elements of a clinical trial they wish to do remotely and which they prefer to do in person. Since one size does not fit all, flexibility of modules is important; for virtual and hybrid trials to be effective and efficient for patients and physicians, options must be available.

It starts with trial design. Historically, scientific rigor guided the creation of protocols without flexibility in mind—and for good reason. However, the clinical research enterprise must innovate to ensure it can meet the needs of participants, and virtual or hybrid trials offer the opportunity for real-world evidence like never before. Clinical trials teams can maintain vigilance to scientific rigor while also ensuring there are valid and reliable options that suit multiple participants’ needs.

The Human Element is the Key to Survival

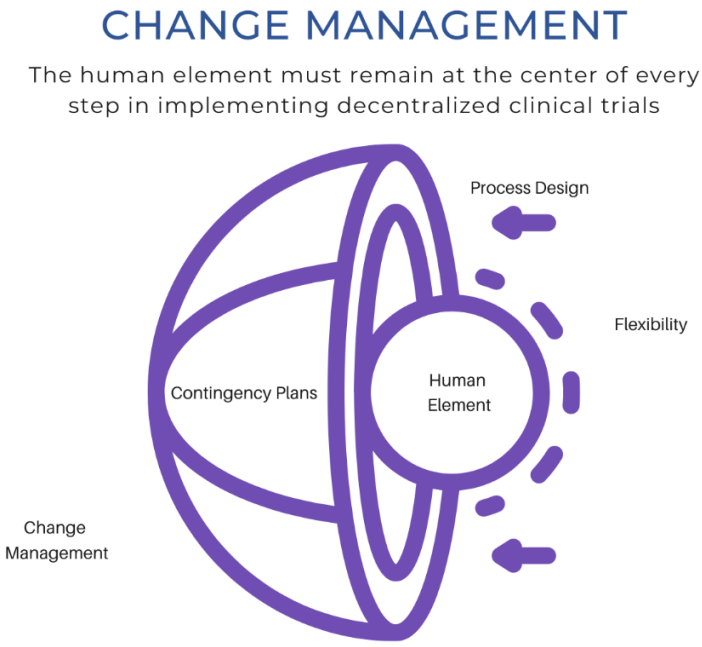
It is unclear how long various restrictions and lockdowns will last, and the long-term ramifications of the pandemic on the world remain unknown. Study teams and research participants are accustomed to in-person interactions. Loss of interpersonal contact accompanied by the mental stress of losing touch with family and friends, job loss, virus fears, and continued health issues may become overwhelming for even the strongest people.

It is important to underscore that technology is just the means to an end. Like education, the relationship between patient and physician is also key, and this relationship can be enhanced in a virtual world by providing modular options. Approaching the transition in a holistic way, including mental health, is of paramount importance.

“People want to feel listened to. Aside from devices or internet service, we need to make a concerted effort from the very beginning to understand influences the pandemic has had on them and their families,” encourages Professor Andolina.

Clinical research can leverage televisits to maintain face-to-face interaction and the ability to read emotions such as sadness or physical symptoms like fatigue. As live video is used to maintain relationships with colleagues, family, and friends, comfort levels with digital interaction in the healthcare space will grow. Additionally, as patients transition more of their ongoing healthcare management to virtual care, their expectations about virtual options for research participation will continue to grow.

It is clear that the access, skills, process, socioeconomic, cultural, and mental health challenges of the remote education transition mirror those of clinical research. If these lessons from the classroom are applied to keeping the human element at the center (as illustrated below), research teams can make the transition more successfully and be ready for the next hurdle because, in the words of Heraclitus, “Change is the only constant.”



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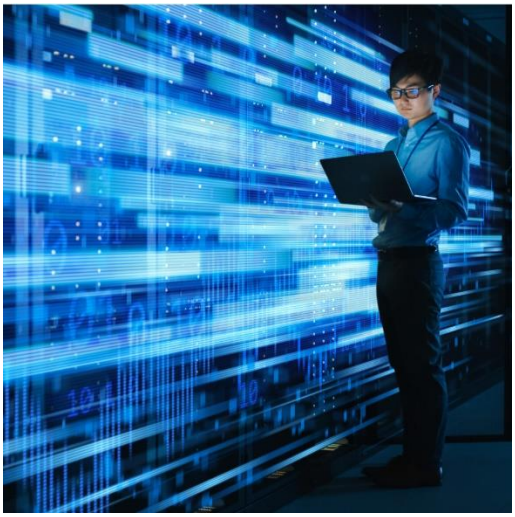
DATA-TECH CONNECT

Clinical Goes Digital to Bring Medicines to Patients Faster

Henry Levy



In response to COVID-19, the clinical research enterprise has made Herculean efforts to minimize disruption and accelerate clinical development in the past year. From simpler trial designs and faster protocol development to decentralized trials that digitize specific trial processes, there have been countless examples of life sciences companies and health authorities coming together to innovate and collaborate more efficiently.

We expect to see acceleration across clinical development as more companies shift to modern, digital applications over manual, paper-based processes in 2021. We're already starting to see this happen with the growing adoption of solutions that enable virtual visits. The efforts are streamlining trial execution and lowering the patient burden of participating in studies.

Looking ahead, transformation in the clinical space won't slow down. Trials will continue to advance toward paperless, patient-centric approaches—streamlining processes for sites and expanding a study's reach to new patient populations. Companies will modernize data management to meet new regulations. Real-world evidence will make contributions to clinical studies and improve the development of products. Here are three predictions about changes to watch for in the industry in 2021 and beyond.

Paperless, Patient-Centric Trials Will Drive More Effective Clinical Development

Getting participants to finish a clinical trial has never been easy due to the heavy burden placed on them. In 2019, dropout rates rose to 19% in late-stage studies globally from 15% in 2012,{1} and COVID-19 disruptions and restrictions have only deepened the need for change as the industry looks to end its reliance on paper.

In response to these compounding factors, paperless, patient-centric trials will be a top priority for life sciences companies to reduce the patient burden, provide more access to trials, and modernize studies. Whether through an electronic consent process, remote data collection, or virtual visits made possible in a decentralized trial model, there are numerous ways we'll see sponsors, contract research organizations (CROs), and sites make it easier for patients to participate in trials while improving stakeholder collaboration over the course of a study.

The digitization of trials will also help enhance the diversity of patients participating in them by expanding the reach and access of studies. Sponsors can help spearhead this effort toward greater diversity by specifically seeking out research sites in underrepresented geographies, while CROs can invest in more support for investigators in areas with minority populations.

By giving patients an easier way to participate in clinical trials and showing them their commitment to diversity in the coming years, life sciences companies will improve study outcomes and drive more effective clinical development.

Clinical Data Management Modernization Will Accelerate to Meet New Regulations

Increasing regulations from the U.S. Food and Drug Administration (FDA)—and more recently, the European Union Medical Device Regulation—have created a new sense of urgency for medical technology companies to improve data collection and analysis. Manual processes and legacy systems are no longer going to cut it if companies want to ensure compliance, reduce risk, and allow for innovation moving forward.

As a result, we expect to see the industry shift toward more connected and transparent ways of managing its various forms of clinical data next year. For example, more robust, modern

infrastructures will help companies track, analyze, and share much larger and diverse datasets stemming from more complex studies—both pre- and post-market.

In this new world, where data collection is never going to stop and regulations will continue to evolve rapidly, the companies that invest in more modern approaches to clinical data management will have the agility they need to adapt for the future.

Real-World Evidence Will See Real-World Application

While the industry has been talking about using real-world data in clinical trials for more than a decade, it wasn't until within this past year—with the urgency and rapid digitization brought on by COVID-19—that companies finally began viewing it as an essential, rather than as a merely nice-to-have, capability.

Computers, mobile devices, wearables, and other biosensors hold a wealth of information about patients. From sleep quality and heart rate to step count and calories consumed, there are various lifestyle-related datapoints that study administrators can now use to supplement the data they're collecting in a controlled setting.

With the FDA and other regulators now starting to accept this type of real-world data, we see an exciting opportunity to improve product development, health decisions, and diagnostics related to all therapeutic areas. While these are certainly still early days for the "new normal," the infrastructure, regulatory environment, and technology have all reached a place where real-world data can scale and consistently contribute to clinical development.

The Industry Accelerates Toward Modern, Connected Clinical Research

The impact of COVID-19 was felt across the industry. More than 100 companies reported disruptions of their clinical trials,{2} and more than 1,900 studies have been affected.{3} The industry accelerated modernization efforts to enable virtual visits, remote monitoring, digital ways of collecting data, and more to ensure trials remained on track and to start new trials fast.

Sponsors, CROs, and sites are entering an era in which clinical development will be much more connected, digital, and streamlined. Clinical teams will be able to work more efficiently and

faster, and patients will have more access to, and choices for participating in, trials. While the challenges experienced in 2020 will be unforgettable, the future for clinical trials is brighter than ever.

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RECRUITMENT & RETENTION

Clinical Trials Have Put Patients at the Center—But What About Caregivers?

Jennifer Price

Patient centricity is now a key focus area for clinical trial sponsors and clinical research organizations (CROs) eager to develop better protocols, support more inclusive study designs, and increase participant engagement from recruitment to study close-out.

Whether it's patient-centered study design, focus groups, satisfaction surveys, rapid reimbursement, or remote reporting, sponsors are devoting a tremendous amount of effort to attracting and retaining study participants. This is to be expected, as clinical trials comprise nearly 40% of the research budget for U.S. pharmaceutical companies, but come with an average study dropout rate of 30%.

Still, a crucial factor in the success of patient-centric activities seems to have avoided gaining notice to any significant degree in many trials, and that's the factor inherent in the patients' caregivers.

The Missing Element of the Caregiver

While the shift to greater patient centricity in clinical research shows promise, valuable benefits to the success of trials can also be gained through consistent, thoughtful focus on caregivers. Caregivers (also known as carers, caretakers, or guardians) provide direct care to the chronically ill, elderly, or children. They can be parents, relatives, and other individuals who are the support system for the patient.

In the U.S., there are nearly 40 million caregivers providing care to the 16.6% of American adults aged 18 and above who have a disability or illness. This percentage is similar or higher depending on the country selected. For many patients, their quality of life—even their survival—depends upon their caregiver's ability to recognize when they require increased or supplemental support and act as necessary.

A patient's participation in a clinical trial often hinges on the caregiver's ability to provide transportation for site visits, administer medication, and collect necessary data. This can make caregivers just as important a factor as the patient in determining whether that patient can successfully participate in a clinical trial from screening and informed consent through to its conclusion.

The quality and quantity of data collected for a clinical trial often are as dependent on the caregiver as on the patient. However, caregivers too frequently receive relatively little support and attention throughout clinical trials.

Key Issues that Create Caregiver Burdens

A major obstacle that makes it difficult for caregivers to help their patients participate in clinical trials is transportation. Simply getting the patient to the trial site can be extremely challenging. Not only can the patient's disability make travel prohibitive, hours spent on the road or in the air may require taking time off from jobs or away from other obligations. Consequently, many caregivers who are working spouses and/or parents are unable to consistently bring patients to and from clinical trial sites.

For caregivers of patients suffering from disorders such as Duchenne muscular dystrophy, travel burdens can be particularly acute. Duchenne patients become non-ambulatory in their teenage years and require round-the-clock care. This makes travel in general more difficult. Since Duchenne is a relatively rare disorder, affecting approximately one out of every 5,000 live male births, clinical trials are limited in number and conducted at specialized medical centers around the country. Many families who do not live close to one of these centers may not be able to travel to these sites or take time off from work.

Caregivers also may be the critical factor in collecting quality data and adhering to a trial protocol. They may be required to provide a complete medical history of the participant at the onset of the study, as well as ongoing reports regarding medication schedules, adverse events, and patient data captured from monitoring devices. The trial's efficacy may also depend on caregivers adhering to a strict schedule for administering medications and collecting/reporting data.

For caregivers whose patients are in extended trials, data collection and protocol adherence can be crushing obligations that may have severe adverse effects on their lives and mental well-being. In a 24-week, randomized trial to assess whether meditation would improve the quality of life and ease the psychological stress on caregivers of dementia patients, caregivers who were informed that free respite care would be provided to their loved ones while they were attending study assessments and classes were more interested in participating than caregivers who weren't given this option. The latter group identified lack of respite as a key disincentive to enrolling in the trial.

How Studies Can Better Support Caregivers

There are several ways designers and managers of clinical trials can make it easier for caregivers to facilitate these studies.

Incorporate the caregiver role from the outset. The fact that caregivers are primary contributors of data for a clinical trial should be made clear in educational materials at the beginning of the study. Their concerns and suggestions should be heard during the planning phase to ensure barriers to obtaining data are minimized or eliminated. If caregivers advocate for hybrid or fully decentralized clinical trials (DCTs), such preferences should be considered depending on study requirements.

Target caregivers in recruitment efforts. Research recruitment typically is targeted to patients, not caregivers. For many potential participants who are unable to search the internet for appropriate trials, their caregiver is the person who will reach out to the study team. It is important to keep caregivers in mind when developing recruitment strategies such as marketing

to the right audience and providing study-based recruitment websites that can be easily found online.

Emphasize ease and transparency of the consent/assent. Provide a targeted consent/assent to the participant and to the caregiver with specific language for the caregiver, allow them to ask questions, and give them appropriate answers. This can be done during a telehealth virtual visit with the study team that includes all caregivers, so they receive consistent information at the same time as the study participant. Consent/assent can be collected electronically using any phone or tablet device. Allowing this to be done in a comfortable home setting eliminates any anxiety or complications associated with traveling to a medical facility.

Adopt and discuss the benefits of a hybrid or fully DCT approach. Explain to caregivers the benefits of hybrid and DCTs model compared to a standard clinical trial design, including frequency and ease of remote data collection, enhanced data quality, and decreased burden from eliminating or reducing some travel to trial sites. While these approaches may be new to caregivers and patients who have participated in trials featuring other designs, the use of mobile technologies and other practices to increase ease of participating will prove to be a selling point for studies.

Benefits of a Caregiver-Centric Approach

By improving recruitment practices and reducing barriers to participation such as required site visits, clinical trial leaders can improve study recruitment, engagement, and retention. They also can promote greater inclusivity and diversity of ages, races, and disabilities, which historically have been shortcomings in clinical trials.

A 2019 study published in *JAMA Oncology* analyzing 230 clinical trials from 2008 to 2018 that led to cancer drug approvals by the U.S. Food and Drug Administration concluded that "black and Hispanic races are consistently underrepresented compared [to] their burden of cancer incidence." Improved diversity is needed in clinical trials and can be achieved as caregivers are better considered and supported.

When clinical trials put patients *and* caregivers at the center of their studies, they can improve the clinical research enterprise's patient-centric focus with a positive impact on overall engagement, data quality, and research outcomes.

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PRESCRIPTIONS FOR BUSINESS

Increasing the Impact of Innovative Adherence Research with Digital Medication Adherence Monitoring

Bernard Vrijens, PhD

Clinical researchers based in academic medical centers, private practice study sites, NGOs, or foundations know how crucial it is to monitor and manage patient medication adherence in a clinical study or research setting. According to the World Health Organization, up to half of patients with chronic diseases fail to take their medications properly.{1} Research shows many patients who are part of clinical trials do not maintain medication adherence either, despite being closely monitored.{2}

Historically, these protocol deviations have often gone undetected by the more traditional non-digital measures of adherence, such as pill counts, blood sampling, and patients' self-reporting, as they inherently lack the precision to do so. Some of the most common culprits that prevent medication adherence from taking place include:

- Poor communication between the healthcare providers and patient.
- The patient having limited knowledge of the drug and how to use it.
- The patient's fear of suffering adverse effects or side effects.
- The patient not agreeing that he or she needs the medication.
- The patient misunderstands complicated medication routines.
- The patient perceives no benefit from the medication.
- The patient forgets to take the medication.

Academic researchers work tirelessly to prepare the protocol of a study investigating medication adherence. Crucially, the method to measure medication adherence can highly impact the results and conclusions. Electronic monitoring of dosing history using a medication event monitoring system offers enhanced benefits. Electronic compilation of dosing history data, enabled through such systems by smart packages, is an effective way to monitor, identify, manage, and document the risks associated with poor patient adherence to medications in the research setting.

The Benefits

Digital medication adherence monitoring is straightforward and easy to implement in an academic clinical study without delays, and is applicable to all study participants with minimal burden for the patients. Patients are empowered as the solution is usable without any necessary configuration by patients. Such innovations are non-intrusive and friction free for patients. There is no need to combine an app or phone, nor to recharge/change the battery.

The analysis of medication adherence data collected using smart packaging enables researchers to:

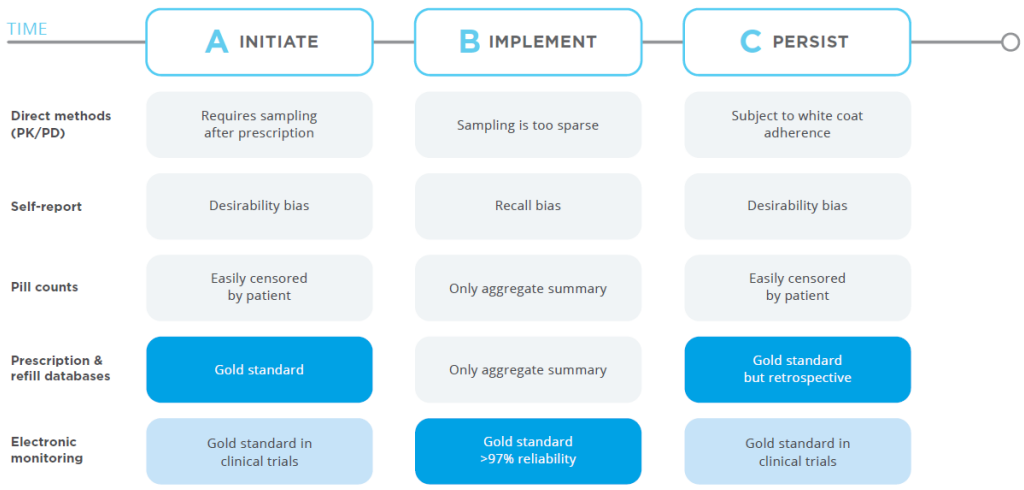
- Quantify medication adherence and differentiate its three elements (initiation, implementation, and persistence) as suggested in the Medication Adherence Reporting Guidelines (EMERGE).{3}
- Assess the determinants of patient non-adherence to medications and determine the causal pathway between suboptimal drug exposure and outcomes.
- Manage medication adherence in individual patients by providing feedback on the patient's drug dosing history, showing occurrences of errors that can jeopardize treatment outcomes.

Eliminating Bias in Results

Non-electronic methods like pill counts, blood sampling, and a subject's self-reporting remain widely used, but do not allow researchers to distinguish between the three elements of medication adherence, tend to overestimate medication, and can thus bias the results of adherence research.

The following figure highlights how the different methods vary.

Figure 1: Measures Used to Help Monitor and Alleviate the Issue of Non-Adherence to Medications



A Review of the Literature

A panel of international experts concluded that electronic monitoring is the optimal measurement approach for the detection of missed doses, extra doses, and wrong time intake.{4} Electronic monitoring is a robust indicator with error rates of <3% in research settings and clinical trials of when the patient took the prescribed dose of the drug.{5}

Compared to electronic monitoring, adherence is significantly overestimated using self-report, pill count, or healthcare provider rating. Those pre-electronic methods are sparse and biased, leading to sloppy estimates of medication adherence.{6} Based on records from ClinicalTrials.gov, between 2017 and 2019, 150 National Institutes of Health (NIH) research grants examined adherence to prescribed medications in which the combination of self-report and MEMS® Caps (a specific marketed type of medication event monitoring system) or other electronic monitoring system were the most common measurement approaches.

Medication Event Monitoring Systems (MEMS®) in Action

Many researchers are improving the power of their research and increasing the success of publication by adopting reliable state-of-the-art measurement systems of patient adherence to medications, as demonstrated in the following examples:

Example 1: Report of a MEMS® study led by the Ruedi Lüthy Foundation (formerly Swiss Aids Care International), Bern, Switzerland (2019, unpublished){7}

"According to the study results, MEMS® provides a better assessment of adherence levels when compared to the pill count method or self-report. Assessing adherence with MEMS® was a better predictor of viral load outcomes compared to use of pill counts. Clinicians should not use pill counts as the sole adherence assessment technique in adolescents as it is vulnerable to manipulation."

"… pill count method, which is the most frequently practiced method to estimate adherence, was shown to grossly overestimate adherence. Since pill counts were discrepant to MEMS® results, we can assume that adolescents frequently dumped their pills so that they would appear as being adherent to their medication."

"MEMS® had the widest distribution of adherence levels as compared to the pill count method. Only adherence measured by the MEMS® was significantly associated with the clinical outcomes of participants hence the MEMS® was shown to be a better predictor of adherence in adolescents on ART."

Example 2: Feedback posted on ClinicalTrials.gov from a study coordinator who participated in a study led by the RAND Corporation in 2020

"[P]atients appreciate the MEMS® and love them to the maximum. Some of the patients were not willing to surrender the MEMS® back [because] they think without the MEMS®, their medication adherence will drop. …Almost all agree that [this type of medication event monitoring system] helps them to take their medication well in a sense that it will report them if they don't take their medication…. …In most cases, MEMS® adherence moves in the same direction with someone's health. Patients who show high MEMS® adherence also tend to have a low viral load. I am therefore confident that these solutions are really helpful to enable researchers do their work, but they are in themselves very helpful in motivating users to improve their medication uptake."

Conclusions

Patient non-compliance with, or non-adherence to, medications is an important factor that can put the success of a clinical trial at risk. Medication event monitoring systems present a proven solution that is straightforward and easy to implement in any study. The method is applicable to all study participants without additional burden for the patient. In addition, it is a mature solution with track records in more than 1 million patients in research settings, including at more than 500 universities and research centers worldwide in more than 1,000 clinical trials.

In today's research settings, solutions are needed that seamlessly measure and analyze patient medication adherence to support successful management of patient adherence to medications. Overlooking this risk can lead to significant issues; however, they can be easily diminished by implementing a mitigation plan based on proven digital medication adherence monitoring systems to maximize the chances of success to the study. Medication event monitoring systems have been a part of successful adherence research for more than 30 years, increasing the impact of academic research findings.

For more information on how medication adherence solutions can improve research and mitigate the effect of non-adherence, visit https://www.aardexgroup.com/services/academic/.

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CAREERS & CULTURES

Now Performing in the Biotech Big Top: The Chief Medical Officer

Rosalie Harrison

It often seems that, when talking with chief medical officers (CMOs) about their work, circus metaphors abound. “It is like this,” one CMO told me, “I am trying to balance many plates, but none of them are spinning.” Another confided, “I feel like I’m juggling with fiery torches” and yet another described her work as “performing on a trapeze with absolutely no net.”

Despite these challenges, the allure felt by some physicians working in drug development with well-established (and perhaps somewhat traditional at their corporate age) sponsor companies to “run away” to join a shiny, new biotech as its CMO is undeniable. Feeling trapped in endless meetings and a constant battle for project-funding relevance—or simply tired of waiting around to move to the next rung of the ladder—MDs may be drawn to roles that promise hands-on, strategic impact and the possibility for more agile decision-making.

The allure is particularly strong, of course, where the coveted (and often romanticized) role of CMO is concerned. Like merely visiting the circus, however, biotech fantasy does not always prepare one for biotech reality. While most MDs are quite quick to appreciate the need for innovative science and clinical pipeline potential when assessing a biotech opportunity, the importance of other game-changing challenges often goes unexplored or is simply misunderstood.

If you are an MD in this situation, equally important is the self-awareness needed to assess whether "circus" life is right for you. Offered here, for MDs considering a biotech career move and CEOs/Board of Trustees looking to hire the right CMO, are some additional factors to consider.

Seaworthy Mates Matter

When you leave big pharma to join a start-up biotech, it's actually more like you've run off to sea rather than to the circus. You are stepping off a stable aircraft carrier and landing in a life raft. Don't be in denial about your newfound situation; you will be subject to severe and changing weather conditions. To survive, everyone in the life raft must be able to collaborate and align, and to do so in extremely dynamic conditions. Unpredictable stress behaviors will abound, even for the most seasoned leaders.

In such an environment, trust, respect, and shared vision and values are essential for survival. Accordingly, we recommend that, in addition to assessing the experience of the leadership team you will be joining, you conduct a "life raft" gut check. It's a simple process—before jumping ship, ask yourself if these are the people with whom you would want to share a life raft. Listen to any nagging doubts and act accordingly.

Role Respect is Vital

As the CMO, you will undeniably be a critical moral and ethical compass for the company. Do not underestimate the commercial and investment pressure that will bear down upon you while your medical ethics responsibilities are ramping up exponentially. Your ability to safeguard and perform this function is of the utmost importance to the integrity and success of the company, not to mention the rights and safety of patients.

You will also have fiduciary duties to investors. As such, the structure of the CMO role must have adequate strategic input and cross-functional responsibility for you to perform. You must also ensure that the CEO and Board have full respect for, and understanding of, the function that a CMO must serve. Do not compromise on these issues when interviewing, conducting your due diligence, or even in the final stages of negotiating the terms of your role.

An SOP Void Can be Disorienting

You will undoubtedly confirm during your interviews that you are capable of wearing many hats and being hands-on. We even believe you will be sincere about it. However, especially if you are coming from big pharma, it's likely you have no idea what this really means.

Gone are the standard operating procedures (SOPs) and systems that were as foundationally reliable as the air you breathe. Even though you will be tasked with building sustainable frameworks—capable of moving your development pipeline closer to the patient—it is altogether possible that you will be the only one in the room who even knows what these SOPs and systems are and/or why they are important. So, forget about the safety net.

Wearing many hats and being hands-on is more akin to performing on the trapeze while building it. A need to adhere rigidly to (known) process and policy is one of the primary reasons professionals fail in an entrepreneurial, fast-growing environment. You must build a framework that is regulatory- and safety-compliant, but you will need to do so with innovation, agility, and more-with-less thinking, all of which will be critical to your success (and sanity). Do not underestimate your own risk profile and resilience in this regard.

You Will be Creating Company Culture

The reason big pharma companies feel like stable aircraft carriers is not just because of their size or their reliable SOPs; stability is also greatly enhanced by the presence of a well-defined and implemented company culture. As a member of the C-Suite, defining and implementing company culture will now be in your hands.

Creating a company culture is a critical strategic responsibility. It is essential to cultivating shared purpose and fostering organizational vitality, especially in a dynamic environment where culture can be impacted by the personality of every new hire. It is also essential to employee retention and engagement—the life blood of any biotech.

This is an exciting and daunting responsibility, and it is often overlooked. Culture does not just happen—it's strategy, though it can feel like a soft skill that should be relegated to the human

resources office (a sophisticated function that might not yet exist in your biotech). Think again, and be sure you will enjoy this aspect of the role.

Recruitment, Recruitment, Recruitment

A huge part of your CMO job will be recruitment. Being dynamic, fast-paced, and eager for go-global growth is a hallmark of the kind of professionals it takes to move a pipeline from early- to late-stage development. Entire functions will need to be significantly upgraded or created and new geographies will need to be explored.

Professionals with experience at launching products and in full command of all the commercially aware skillsets that requires will be needed to supplement a workforce that has, up until now, gotten by on the strengths of its scientific innovations. Attracting and integrating critical new talent while valuing your existing contributors—many of whom may hold inflated biotech job titles and below market salaries—will be extremely challenging.

You may, in fact, find that your recruitment power and support are significantly less than you expected in such situations. When assessing your fit for a CMO role, make sure that building your organization under these circumstances feels professionally rewarding and worthwhile, rather than daunting. It will be a big part of your job.

Nothing Survives Without Money

A biotech can have amazing science and a promising pipeline potential, but without an appropriate financial strategy the company will not survive. Take time to assess historical and current capitalization, as well as the company's continuing ability to attract and secure capital in the future, whether through investors or alliances. Pre-commercial biotechs do not survive without money.

You Are Embracing a New Career Path

A biotech career is very different from a traditional big pharma career. When assessing a move to biotech, you will need a new career mindset. You are investing in potential and your compensation package will reflect this reality and risk.

In addition, many (if not most) biotechs are destined to fail or get bought out, so it is not unusual for professionals who transition into biotech to grow their entrepreneurial leadership competencies through multiple career transitions. If you can embrace this new mindset and still find yourself excited about the new challenges and opportunities, circus life may just what you needed all along.

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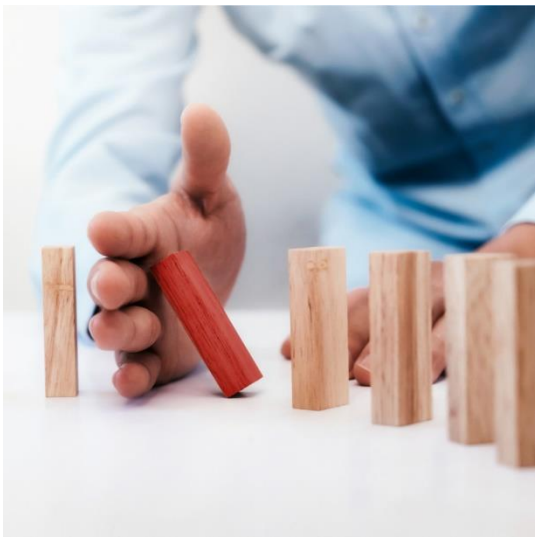
THE LEGAL LANDSCAPE

Risk Allocation for Clinical Trials: What You Need and Why

Robert King



There are dozens of issues that can slow clinical trial negotiations. Among the worst offenders are "risk allocation" clauses. These clauses define who is financially responsible when something goes wrong.

In Clinical Trial Agreements (CTAs), the main risk allocation clauses are the "indemnification" and "subject injury" clauses. Damages under an indemnification clause are potentially larger, but less likely to occur. Payments under subject injury clauses are made immediately, while indemnification liability will happen years later, since it only occurs following litigation.

A sponsor's initial CTA offer will always include an indemnification clause, but only rarely include subject injury protection.

Here are how the clauses might play out in the "real world," and an explanation of why institutions need to ask for subject injury protection.

The Intricacies of Indemnification

A subject is administered medication onsite, then, while driving home he passes out. His car crosses into oncoming traffic, hitting another car carrying a family. Two people are killed and another paralyzed. There is significant property damage.

The outcome would probably look like this:

- Multiple plaintiffs and defendants.
- Numerous legal theories and categories of damage might be claimed (e.g., property damage, medical malpractice, products liability, loss of earnings, mental anguish, medical expenses, pain and suffering).
- The damages could be massive.

The case(s) could be tied up in court for years and, depending upon the allocation of blame and who actually paid out damages, the indemnification clause *might* be relevant. Small claims, for example a case involving only a $10,000 medical bill, will not generate indemnification claims because the plaintiff's counsel would be unlikely to take on the case. The work required just doesn't justify the potential payout.

Sponsors offer indemnification protection because the market requires it; indemnification payments are unlikely; when they do pay, the payment is years later (minimizing political repercussions); and any damages may be covered by insurance.

When developing a strategy for indemnification clauses, an institution should start by considering the following issues:

- In most instances, an institution can refuse to indemnify a sponsor, but it may take some hard negotiating, so the risk of damages should be weighed against the potential delay in reaching agreement.
- A sponsor's indemnification obligations should be reduced to the extent that any of the indemnified entities contributed to the damages. In plain English, it should not matter if it was the institution or the institution's contractor whose misconduct contributed to the judgment. An indemnification clause that threatens reduced payments for misconduct, including contractor misconduct, will incentivize the institution to supervise its entire team carefully.
- Many states ban public institutions from accepting indemnification obligations. When an institution says it cannot indemnify, the underlying statute should be examined.

Frequently, the institution will fail to mention that it does not quite fit the standard for entities covered by such a ban. Institutions do not expect to get caught on this issue, and when they are caught, they tend to fumble about and then claim that indemnification is against their "policy." This is a vastly different conversation because "policy" is legalese for "I don't want to do something, but I can." In this scenario, one can expect that it will be difficult, but not impossible, to get internal approval from the institution. The issue shifts from a non-starter to how much effort is the sponsor willing to expend to get indemnification protection.

- Indemnification clauses will often include a hard notice requirement. If there is a hard deadline, an institution should always include language to the effect that, if the deadline is missed, the indemnification obligation will only be reduced by the extent that missing the deadline prejudiced the indemnifying party's ability to defend the case.

Remember, an indemnification claim can be for a great deal of money. Given the opportunity, like a slightly missed deadline, the opposing counsel will be looking for any argument that will avoid payment being made. By forcing them to show actual prejudice, dodging payment is made more difficult.

Subject Injury

Subject injury payments are more likely than indemnification payments, but they tend to be for less and occur earlier than indemnification payments.

Sponsors are not legally required to pay for a subject's medical care arising from adverse events. If a subject requires treatment, he or she is financially liable. Further, if the subject cannot afford medical care, then the medical provider is at risk of non-payment. By adding a subject injury clause, the sponsor assumes this risk; no litigation is required, and the institution simply issues an invoice.

Few sponsor templates include a subject injury clause. Sponsors often claim the clauses are unnecessary since indemnification clauses provide adequate protection. However, this ignores the long payment lag, the need for litigation, and the fact that small claims are unlikely under an indemnification clause.

The real reason that sponsors do not offer subject injury protection is practical and political. Sponsors want two things—data as quickly as is feasible and budget certainty. No one enjoys having to explain away cost overruns.

Think about a $10,000 claim. It is probably too small for litigation, so indemnification is irrelevant. However, that same claim would be paid out under a subject injury clause. Given the greater likelihood for many claims, the subject injury clause undermines the sponsor's financial certainty, and it puts the current clinical team in the position of having to explain cost overruns.

Institutions *must* insist that a subject injury clause be included in the CTA. Once a subject injury clause is included, the discussion will turn to how the proper payment amount will be calculated.

How much patients are charged for care varies wildly depending on the subject's insurance. Two years ago, I was admitted to a suburban Philadelphia hospital for four days. Because of a clerical error, I was listed as uninsured and was billed $78,000. Luckily, I had Blue Cross, so my bill was immediately reduced to $16,000, which was their "negotiated rate." Once submitted, Blue Cross paid out all but $4,500.

Was I happy? Of course not, but I was a heck of lot happier than if I had owed $78,000.

If I had been a trial subject who had an adverse event, which amount owed would be appropriate? A sponsor that is going to offer a subject injury clause must consider the following issues:

- Should the institution be required to submit an insurance claim prior to asking for sponsor payment?
- What is the impact if the subject had Medicare or Medicaid?
- How does the sponsor accepting financial responsibility impact its reporting requirements?
- What are the penalties for failure to comply with reporting regulations?

An institution will want the payment to be what is "customary," since it can then charge more for an uninsured subject (e.g., $78,000). On the other hand, a sponsor will want the rate for any reimbursement to be "reasonable," as this allows it to "bargain" with greater leverage.

In Summary

Any institution conducting sponsored research with human subjects that fails to obtain a subject injury clause in a CTA is at significant financial risk. Once the sponsor includes the clause, the institution should obtain the most detail feasible, because any ambiguity increases the likelihood of the sponsor delaying or reducing payment.

Robert King (Robert.King@tpclinical.com) is an attorney with more than 20 years of healthcare experience and founder of TakePoint Clinical, a firm whose credo is that "Medical Research is Too Important to Wait on Endless Negotiations." A white paper offering step-by-step instructions on how to speed clinical negotiations is available for download at the firm's website.

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TRIALS & TECHNOLOGY

Using Natural Language Processing to Improve Clinical Trial Design and Patient Safety Performance

Jane Z. Reed

The drug development process is lengthy, complex, and expensive, which is why it's important for pharmaceutical companies to explore innovative technologies that can address bottlenecks and provide efficiencies. Clinical trials are one of the most expensive stages of drug development, and thus a key focal area for improvements.

Improving clinical trial performance starts with selecting the right patient populations for inclusion. Additionally, effective mechanisms for identifying adverse events in near-real-time are important for minimizing disruptive patient safety events. These processes have become increasingly challenging as the amount of available health data proliferates. According to Dell EMC, healthcare organizations have seen a mind-boggling 878% growth rate for health data since 2016.

This surging amount of health data, coupled with its complexity, has made it nearly impossible for humans to properly analyze data before, during, and after clinical trials without leveraging technology. To efficiently develop new drugs, pharma companies must process, sort, and share data at speeds and volumes that exceeds human capacity.

To help manage this avalanche of data, more pharmaceutical companies are turning to natural language processing (NLP) technology to mine unstructured, text-based documents and convert the data into structured information that can be analyzed by a computer. NLP can help pharmaceutical companies speed development and reduce costs. For example, in advance of clinical trial development, NLP can help to stratify patients, and during trials, NLP can quickly identify patient safety events. The following sections provide real-world examples of how two companies have leveraged NLP to accomplish these important objectives.

Stratifying Heart Failure Patients

Because most diseases are multifaceted, pharmaceutical researchers face challenges in identifying the most appropriate patient populations in terms of response to specific interventions. As a result, most drug developers have adopted a stratified approach to identifying various sub-populations of patients to ensure the most appropriate therapies are tested in clinical trials and applied in broader clinical use.

Properly stratifying patients requires precise, accurate data, and NLP can help researchers unlock important patient data such as symptoms and disease severity from unstructured, free-text fields in electronic medical records (EMRs). For example, Bristol-Myers Squibb (BMS) sought to understand more about patient stratification for heart failure risk. Heart failure patients often demonstrate a high level of clinical heterogeneity, which creates problems for treatment and risk stratification. However, BMS researchers believed that if they could develop a greater understanding of heart failure patients' clinical characteristics, they could improve their understanding of how to best treat different patient populations.

BMS researchers obtained EMR and imaging data from approximately 900 patients and used NLP to capture data on about 40 different elements related to patient demographics, clinical outcomes, clinical phenotypes, and other variables such as ejection fraction and left ventricular

mass. The researchers used that information to identify four classes of patients with discrete clinical and echocardiographic characteristics.

The analysis revealed that the four patient groups showed substantial differences in one- and two-year mortality and one-year hospitalizations. By better understanding how to stratify heart failure patients, BMS unlocked insights that offer the potential improve clinical trial design, identify unmet needs, and develop better therapeutics.

Rapidly Identifying Patient Safety Events

Identifying serious adverse events (SAEs) during clinical trials is a critical part of patient monitoring, but reporting forms are often saved as images or PDFs, making manual extraction of patient data slow and prone to error. To enable a more rapid response to SAEs, Agios developed a workflow to process the report forms by using NLP to extract all relevant patient data.

Creating this workflow involved several key steps, including capturing images of SAE reports, indexing and normalizing all documents with industry-specific ontologies such as MeSH and MedDRA, and using NLP to extract key patient attributes such as concomitant medications, adverse events, date of onset, and lab test results. Finally, Agios loaded the data into a clinical safety database, enabling rapid access to SAE data for researchers.

To cite one specific example of the workflow's application, researchers explored the risk of differentiation syndrome (DS), a rare and potentially life-threatening adverse event that is a complication of first-line chemotherapy in some acute promyelocytic leukemia patients. In a clinical trial of Agios's IDH1-inhibitor AG120, Agios researchers leveraged the NLP-driven workflow to highlight and cluster MedDRA terms associated with DS across the patient pool in the ongoing clinical trial.

Agios' team characterized which adverse events were most likely to co-occur with DS in the patient cohort, which events appeared in only some cases, and which subsets of patients might be more at risk from DS than others. The extracted data enabled clinicians to explore the patterns of symptoms between patients and identify those at risk.

Better Trials Advance Better Therapies

With better, more precise data at their disposal, pharma companies are well-equipped to continue innovating in their drug development pipelines; however, it takes text-mining technologies such as NLP to fully unlock the power of the data they've accumulated. By helping pharma companies improve targeting of patients before clinical trials start and better respond to patient safety events after they've commenced, NLP advances the development of better therapies through more efficient trials.

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OVER THE TRANSOM

New Tricks of the Trade for Trials

Gary W. Cramer

Nothing stays still for very long in the world of technology and best practices for clinical trials, and the companies rolling out their new goods and services aren't shy about broadcasting what's brand new, what's been retooled, and what's on the horizon for research sponsors and sites to consider adding to their arsenals. The sites and sponsors themselves are often keen to be seen as applying cutting-edge tech and practices to their studies.

For your background information and possible use, in this beta test of a new column for occasional appearances in the pages of *Clinical Researcher* I will share tidbits about some of the latest such items and observations to come to my attention (no endorsements implied).

In Search of Streamlining

In a recent techXpo session for the Virtual ACRP 2020 conference (now available as a free webinar replay), representatives from Remarque and Premier Research focused on "dismantling the status quo of monitoring" by "moving toward a technology-enabled approach to trial oversight."

For too long, the idea of monitoring has been mostly limited to clinical research associates (CRAs), onsite monitoring visits, and 100% source data verification (SDV), the presenters said, adding that this approach is time consuming, costly, and ineffective. They endorsed the concept

of leveraging technology to approach monitoring using a holistic, data-driven, and risk-based data strategy plan. In their vision for the future of data monitoring, the process is streamlined in a single system used to assess site performance and overall trial oversight.

A lot of the assumption has been that 100% SDV equals better data quality, but it's been shown that this is not the case, the techXpo session presenters contended. Limited interaction between sites and CRAs and lack of surveillance in between onsite monitoring visits present problems for reliable SDV; however, "there is an idea that if we are doing less than 100%, there will be some kind of fraud in the trial," they noted. In reality, they cautioned, it is very hard to spot fraud when doing 100% SDV and looking at data on a "very micro level."

"We are really beyond ready for a change" from this approach, the experts said. "A transition to a risk-based approach is really the next leap in the industry." The shift should be to a bigger, macro, top-down view of the data, they added, in terms of which data to look at based on high or low risk in a study and focusing on critical datapoints versus all datapoints. The risk-based approach will incorporate all kinds of monitoring practices and roles, and will begin with a definition of quality up front (as in, quality by design), and with the percentages of source data review and SDV being defined from the beginning.

"We should be leveraging technology by consolidating all study data and monitoring tasks in the same system," the presenters concluded.

The Other 95%

Inato says that the current way clinical research is conducted—with sponsors repeatedly tapping the same 5% of available research sites for conducting trials—doesn't work anymore. It's too slow and expensive, and patient diversity is nearly non-existent, the thinking goes. To raise the profile of the remaining 95% of qualified research sites, Inato has rolled out a new trials marketplace in which these sites can search for and get matched to trials that they are not only qualified for, but that also fulfill their interests and patient needs. Inato's current areas of focus (in the U.S. and France) are multiple myeloma, lung cancer, and ulcerative colitis/Crohn's disease.

Mastering the Trial Master File

According to news received last fall, the first independently accredited Trial Master File University (TMF University) intends to have launched its inaugural training series devoted to managing TMFs—compilations of all the necessary documents produced during the conduct of a trial that are key to inspection readiness—by this point in January 2021. Facilitated by LMK Clinical Research Consulting, TMF University is accredited through the International Accrediting Organization for Clinical Research (IAOCR). "Individuals supporting the TMF play a significant part in the success of clinical trials," said Jackie Morrill, PMP, executive director of clinical operations at LMK. To develop the curriculum, LMK dissected different job roles within the pharmaceutical and clinical research spaces and, with IAOCR's input, tailored training options specifically to employees' job descriptions and responsibilities.

Aiming Technology at the Pandemic

As BetterLife Pharma prepared last fall for clinical trials of AP-003, its interferon alpha 2b inhalation therapy for the treatment of COVID-19, it provided details on how it expected to leverage technology to overcome potential challenges of recruiting patients. Noting that the trials have been designed to promote study participation and streamline data collection, BetterLife indicated that participants with mild to moderate COVID-19 would self-identify for potential trial enrollment following COVID-19 testing at testing centers. Trial consent is being obtained virtually and the trial is conducted via telemedicine from the participant's home, with all data collection being accomplished electronically to allowing for rapid review. "[W]e have made significant strides in advancing these trials in Australia," BetterLife CEO Dr. Ahmad Doroudian said in October. "Using new and innovative technology will allow us to be in the vanguard of clinical study design, to easily meet our enrollment goals, and to expedite any potential [U.S. Food and Drug Administration] approval and commercialization of AP-003 for the treatment of COVID-19."

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