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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.

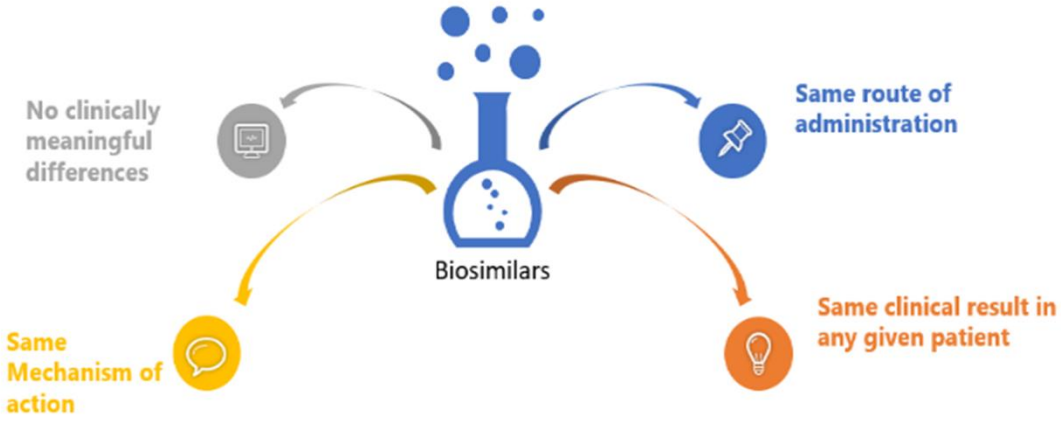
Source:
https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

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

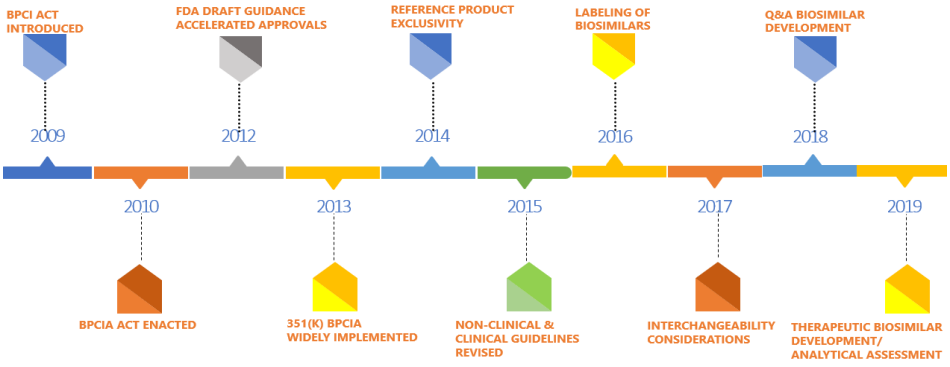
Definitions from the FDA, European Medicines Agency, and World Health Organization[5]

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).

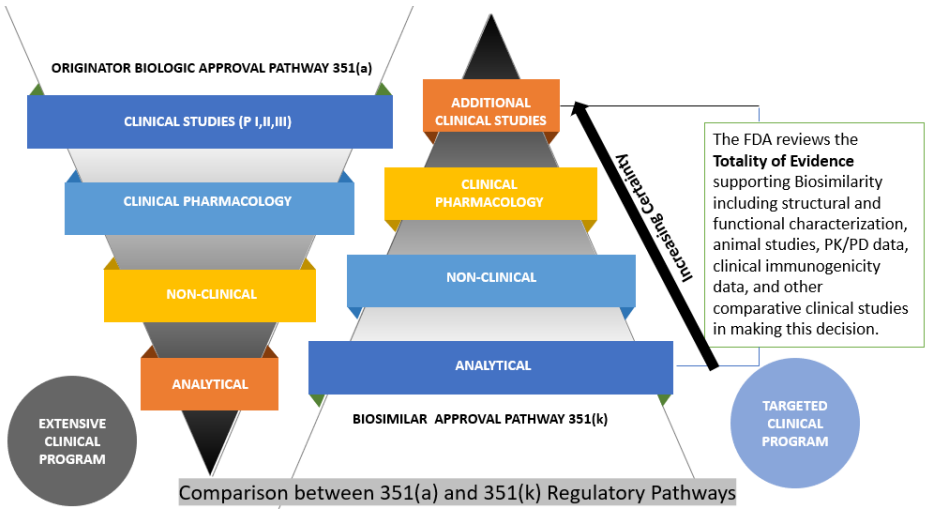
Additional Clinical Studies of Biosimilarity—The objective of a biosimilar development procedure is to validate high similarity between the biosimilar and reference product, rather than separately establishing the safety and efficacy of the proposed product.

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 evidence that the proposed product has highly similar characteristics to the reference product, based on thorough analysis of the reference product and sequential 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

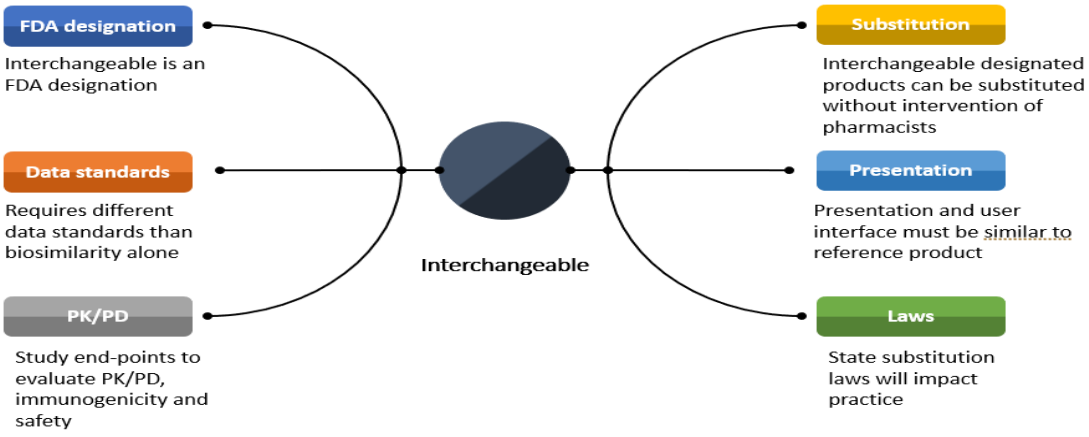
biosimilars at a substantially lower cost. Some of the characteristics that may be considered for extrapolation are summarized below:

- 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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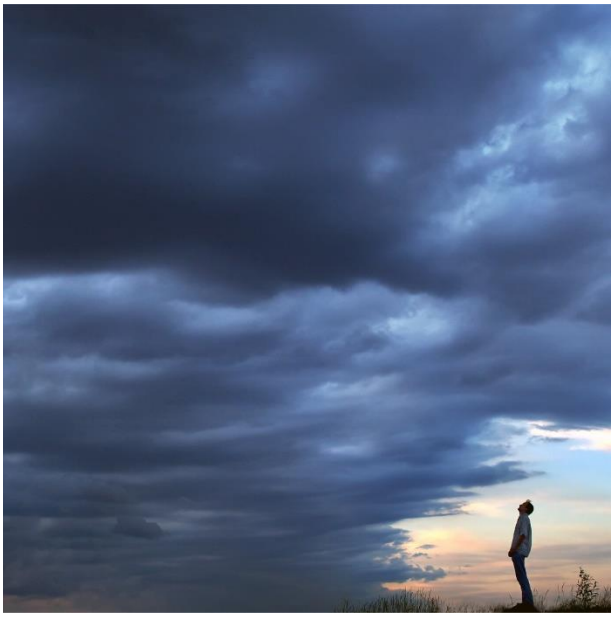
PEER REVIEWED

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

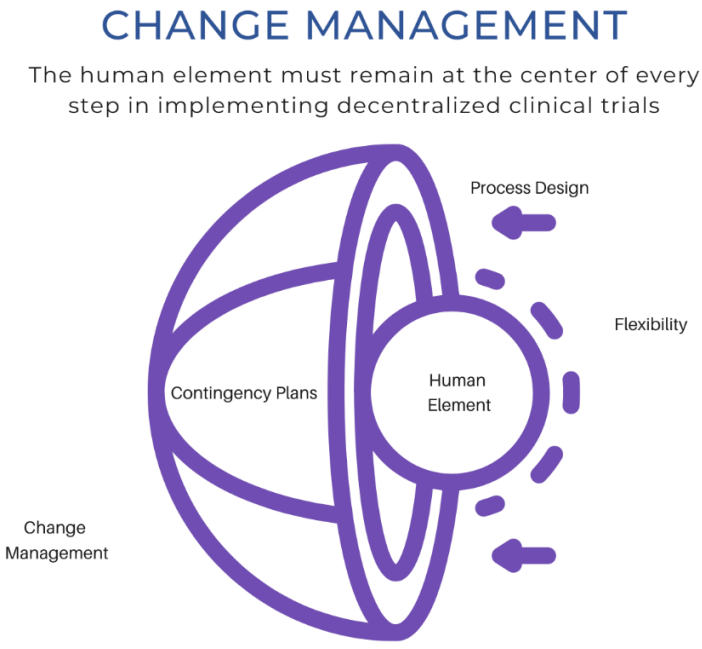
It is unclear how long various restrictions and lockdowns will last, and the long-term ramifications of the pandemic on the world remain unknown. Study teams and research participants are accustomed to in-person interactions. Loss of interpersonal contact accompanied by the mental stress of losing touch 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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CLINICAL RESEARCHER

JANUARY 2021 HOME STUDY

Changed for the Better

Article 1—**The Journey from Biologic to Biosimilar—A Clinical Perspective**

LEARNING OBJECTIVE

After reading this article, the participant should be able to describe the differences between a reference biologic product and a biosimilar based upon it, and to outline the main considerations weighed and steps taken in biosimilar development.

DISCLOSURE

Wasi Akhtar, BPharm, MBA: *Nothing to disclose*

1. What must happen to a trade-name biological product before a biosimilar version can be marketed?

A. Its sales must fall significantly.
B. Its patent must expire.
C. Its efficacy must fail.
D. Its production must cease.

2. Minor changes are allowed between a biological product and a biosimilar one in terms of which of the following?

A. Safety
B. Efficacy
C. Purity
D. Active ingredients

3. Approval of biosimilars in the U.S. is managed through which legislation?

A. The Food and Drug Administration Amendments Act of 2007.
B. The 21st Century Cures Act of 2016.
C. The Patient Protection and Affordable Care Act of 2010.
D. The FDA Reauthorization Act of 2017.

4. What is the term for the concept that a prescriber's intervention is not necessary for a biosimilar to be replaced with the reference product?

A. Equivalence
B. Interchangeability
C. Parallel treatment
D. Bait and switch

5. An abridged approval pathway for biosimilars allows which of the following?

A. FDA approvals in fewer steps than needed for reference products.
B. Study initiations without collection of informed consents from participants.
C. Fewer demands for data monitoring from institutional review boards.
D. Less expensive ingredients to be used when manufacturing the drugs.

6. Each step in the biosimilar approval pathway should do what when compared to the previous stage?

A. Increase the drug's targeted efficacy.
B. Decrease the product's time to market.
C. Increase data monitoring queries.
D. Decrease residual uncertainties.

7. Which of the following is NOT cited as a key concept in the demonstration of biosimilarity from clinical pharmacology data?

A. Exposure and response assessment.
B. Evaluation of residual uncertainty.
C. Totality of real-world evidence and data.
D. Assumptions about analytical quality and similarity.

8. More sensitivity in results is typically considered to be gained through PK/PD studies in which population?

A. Patients receiving placebo only.
B. Healthy volunteers.
C. Blacks and Latin Americans.
D. Patients with underlying conditions.

9. What is the ideal practice for route of administration during in-human PK/PD studies of a biosimilar?

A. It should be different than for the reference product.
B. It should be randomized across the participants.
C. It should be the same as for the reference product.
D. It should be left to the participant's preference.

10. What is the term used when a biosimilar product is approved without further study for an additional indication for which the reference biologic is licensed?

A. Extrapolation
B. Concomitant
C. Equivalence
D. Waiver

Article 2—**5 Lessons for Clinical Researchers from Education's Transition to Remote Learning**

LEARNING OBJECTIVE

After reading the article, the participant should be able to summarize recent developments in, and challenges to, the manners in which remote learning technologies may be applied to clinical research and patient training, as well as to the conduct of home-based clinical trials.

DISCLOSURES

Mary Costello: *Nothing to disclose*

11. What is said to have compounded the urge for an educational focus on study components in clinical research training?

A. The need to raise the study team's profitability.
B. The need to enforce strict medication adherence.
C. The need to upskill staff and patients in technology.
D. The need to modernize staff recruitment practices.

12. The author cites what practice as a way to mitigate challenges when dealing with new technology during clinical studies?

A. Limiting the number of participants at study sites to 100 per study.
B. Ensuring only one "super user" at each site has access to the trial management system.
C. Turning all data collection and entry tasks over to specialized vendors.
D. Utilizing a decentralized trial platform with a single sign-on for all research tasks.

13. What can help staff build empathy for the patient experience with technology?

A. Cross training
B. Role playing
C. Distance learning
D. Mentoring

14. Which of the following does the author say should be reflected in messaging to patients about the use of technology in a trial?

A. Their cultural sensitivities.
B. Their income levels.
C. Their disease status.
D. Their health literacy.

15. The author cites using remote monitoring devices to replace in-person visits for which of the following trial-related needs?

A. Obtaining informed consent.
B. Collecting certain vital signs.
C. Authorizing dosage changes.
D. Updating study protocols.

16. What does the author say a decentralized clinical trial platform should integrate with in the context of a study being conducted?

A. Case report and informed consent forms.
B. Clinical trial agreements and monitoring plans.
C. Wearables and patient-collected data.
D. IRB review timetables and PI delegations.

17. Which of the following are mentioned as items to be updated following any redesigning of processes due to technology and workflow changes?

A. Operating procedures, job descriptions, and performance criteria.
B. Salary levels, certification expectations, and organizational charts.
C. Vendor contracts, consulting fees, and memorandums of understanding.
D. Delegation of authority logs, training budgets, and inspection readiness standards.

18. From whom does the author recommend that feedback on new processes and uses of technology for trials be gathered?

A. Principal investigators and regulators only.
B. Technology vendors and freelance consultants.
C. Patients and staff working on trials.
D. Disease advocacy groups and ethicists.

19. Which of the following are noted as factors that contribute to differentiated needs in online environments?

A. Time zone changes, state-specific limitations, and study blinding.
B. Regulatory guidances, IRB mandates, and PI anxieties.
C. Disease status, site budgeting practices, and sponsor restrictions.
D. Technical skills, site capabilities, and economic hardships.

20. The author mentions which of the following as an advantage of "televisits" between researchers and patients?

A. Being able to conduct "face-to-face" financial transactions.
B. Being able to read a patient's emotions and physical symptoms.
C. Being able to watch a patient's activities 24 hours a day/7 days a week.
D. Being able to see how randomization is conducted.