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Clinical Researcher™

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Research Studies and Studying Research: Designing a Better Tomorrow

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EXECUTIVE DIRECTOR'S MESSAGE

Out of Many, One

Jim Kremidas



We just wrapped up a very productive and inspiring ACRP Association Board of Trustees (ABoT) meeting here at the home offices in Alexandria, Va. We covered a lot of exciting ground, and we'll be sharing the results with you here in the journal, in upcoming messages in other formats, and at our [ACRP 2020](#) gathering in Seattle in May.

For example, we're exploring adding a second regional conference in 2020 because our 2019 event in North Carolina's Research Triangle Park region was such a success on so many levels.

However, instead of talking specifics in this space today, I wanted to focus on the bigger issue of advancing the professionalization of the clinical trial workforce. Our ABoT Chair for 2020, Paul Evans, touches on it in his own message for the journal this month, and the entire board stressed it throughout the latest meeting. In fact, it was something of an unofficial theme of the gathering.

Onward, Research Soldiers

The ACRP organization and its members are dedicated to not only helping individuals thrive in their careers, but to raise the quality bar for the entire clinical trials workforce. It's a strong human calling to want to be part of something bigger than one's self, and I believe ACRP is answering that call by promoting certifications, standards, and other tools critical to giving the ranks of our professionals the respect they deserve.

We aren't doing this alone, of course. In fact, individuals and organizations are seemingly joining forces with us every day. Here are two recent examples we're delighted to share:

Earlier in February, ACRP [welcomed](#) the University of North Carolina at Chapel Hill as the latest member of the [Workforce Innovation Steering Committee \(WISC\)](#).

The WISC is a collaborative partnership of private and public stakeholders working to improve clinical trial quality and to respond to changes impacting the workforce by providing oversight for needed standardization activities. The partnership has led several standardization initiatives in clinical research, including publication of competency guidelines for clinical trial monitors and clinical research coordinators.

Just a few days later, we [announced a new partnership](#) with Pro-ficiency that brings together two of the world's leading providers of clinical research workforce development solutions, and will empower ACRP to provide a next-generation, competence-based professional development experience to its global network of 50,000-plus clinical research professionals and organizations.

Despite the important role clinical trials play in the development of new drugs and therapies, our industry has too often and for too long approached workforce development with a “check box” mentality—ensuring compliance with training requirements, but failing to adequately develop competency or raise the standard of clinical trial conduct. By connecting clinical research professionals and organizations with cutting-edge development programs, this partnership with Pro-ficiency will usher in a new era in workforce development that will fully unlock the potential of our profession.

Lots more good stuff is on the way in 2020! Watch this space.

As always, if you have thoughts or would like to learn about ways you can lend your expertise to your Association's efforts, please don't hesitate to reach out to me directly at jkremidas@acrpnet.org.

Jim Kremidas is Executive Director of ACRP.

CHAIR'S MESSAGE

Show-and-Tell That's Good for the Professional Soul

Paul Evans, PhD



Many years ago when my son was very young, he announced to the whole class in a show-and-tell presentation that his father was a drug dealer. He had been told I was a drug tester because that was easy for a 5-year-old to remember, but I did have an awkward phone call with the Headmaster explaining what clinical trials were and my role in them. It all ended well, and I earned new respect that day from the school management.

Thinking back on that event, I'd like to use this space this month to remind us all to take a step back and remember the broader importance of clinical research and our own contribution. All of us in the drug development industry are literally engaged in life-and-death work. The treatments and devices you help to test and vet are part of a mission you share with other members of the Association of Clinical Research Professionals. It's an exciting mission to protect patients, improve life, and assuage suffering. A higher calling, indeed.

In particular, I'd like to thank the [Academy of Clinical Research Professionals](#), an independent affiliate of ACRP responsible for administration of ACRP Certification exams. It's comprised of trained item writers and currently certified (CCRA, CCRC, CPI, or ACRP-CP) content experts who help shape one of the four exams. Their mission statement makes clear their commitment and contribution to our industry: "Promote and maintain high standards and best practices of clinical research by recognizing those professionals who demonstrate a well-defined competency through valid and reliable credentialing programs."

Academy members work diligently, and sometimes under the radar, to help ensure certifications are reflective of high-quality professional standards. It's no easy task, and they deserve our thanks and praise. Academy members offer us a perfect example of the kind of dedicated volunteers who represent the foundation of ACRP's efforts to elevate the clinical research profession on all levels.

That is one level at which ACRP serves the industry. At another, your Association is also actively working with lawmakers on both sides of the political aisle to better educate them about the value of clinical research and the vital contribution of the clinical trial workforce. ACRP is working to represent you as a professional to help advance both your individual career, and that of the greater industry. I'm sure we'll have more to report on this front in the coming months.

The Academy and our Capitol Hill outreach are just two examples of the way your Association is helping to advance the professionalization of the clinical trial industry. If you are already engaged in one of these efforts, I thank you sincerely. However, if you are new to ACRP or would simply like to learn more about how to become more involved in the greater good of clinical trials, I urge you to learn more from the [About Volunteering](#) page on our website and to contact the ACRP staff listed there, or write to support@acrpnet.org, or call (703) 254-8100 with any questions.

Paul Evans, PhD, is President and CEO of Velocity Clinical Research, and Chair of the Association Board of Trustees for ACRP in 2020.

PEER REVIEWED

Establishing the Link Between Trial Complexity and Coordinator Capacity

Alexa Richie, DHSc; Dale Gamble, MHSc; Andrea Tavlarides, PhD; Kate Strok, CCRC, CCRA;
Carol Griffin



The workforce of the clinical research enterprise continues to change and the demand for experienced professionals at the site, sponsor, and contract research organization (CRO) levels continues to increase. At a national level, there continues to be a lack of qualified professionals for both study coordinator and study monitors. This trend will continue as the appetite for clinical research at a site and sponsor level expands at an exponential rate. At the site level, meaningful assessment of workloads and understanding the capacity of teams are necessary to enhance job satisfaction, retain key talent, maintain high performance, and reduce turnover.

In an earlier article introducing this topic,^{1} the authors described their experience and process in the development of a tool to assess the complexity of a clinical trial in a uniform way across any specialty and study type. Briefly, the first iteration of the tool was comprised of 21 unique elements, each with a possible score of 0–3 points, where 0 = least complex and 3 = most complex (see Figure 1).

Figure 1: Example of Original Complexity Tool

Complexity Tool				
Study Element	No Effort	Minimal Effort (1 point)	Moderate Effort (2 points)	Maximum Effort (3 points)
Active Scoring Elements				
PI expertise and experience with clinical research	N/A	Physician has been lead P.I. on several trials and has a clear understanding of a P.I.'s responsibilities	Physician has been Sub -I on a study(ies) and has enrolled and followed patients on a clinical trial	Physician has minimal research experience and/or requires an increased level of engagement
Study recruitment	N/A	Development of flyers or adding to LCD screens	Community outreach	Specialized recruitment efforts will be required
Target enrollment	0	<20	20 - 100	> 100
Inclusion/exclusion criteria	N/A	1-10 Inclusion/ exclusion criteria	11-20 inclusion/ exclusion criteria	> 21 Inclusion/ exclusion criteria
Informed consent process (initial)	No informed consent	1-10 pages	11-19 pages	> 20 pages
Screening procedures for eligibility (post consent)	0	1-5	6-10	<u>> 10</u>
Screening visit (length)	N/A	< 4 hours	4-8 hours	Over 8 hours
Randomization/baseline cycle 1 procedures	0	1-5	6-10	<u>> 10</u>
Baseline visit/ randomization (length)	N/A	< 4 hours	4-8 hours	Over 8 hours
Personnel required other than the research team, feasibility of the study	N/A	Involves only the research team,	Involves moderate number of different medical disciplines and staff	Involves high number of different medical disciplines and staff, requires more effort and coordination
Procedures needed after baseline/randomization to end of treatment (outside of procedure/drug)	0	1-10	11-20	<u>≥ 21</u>

For example, we included items scored on values such as recruitment strategies, principal investigator (PI) experience, number of screening procedures, number of visits, number of departments involved, frequency of monitoring, and activities at follow-up. An example would

be how a score of 1 would be assigned if a study involved one department, but a study with more than departments including the hospital would score a 3. The total possible score across all items is 63 points.

Additional elements of the complexity tool relate to the overall study design, team engagement, target accrual, consenting processes, length of study, monitoring elements, billing requirements, and if there are any associated ancillary studies.

From there, the research leadership team at the Mayo Clinic in Florida was able to develop a standard based upon natural breaks in the bell curve of the scores. The breaks indicated what would be considered a high, moderate, or low complexity trial design from a complexity standpoint for each clinical research unit.

Development of Version 2 of the Complexity Tool

Through its implementation, the research leadership team quickly identified a key area that could be improved in the Complexity Tool—the elements that were scored were done in such a way that all items were given equal weight. However, many items had a stronger impact than others on the complexity of a study. For example, the amount of data collection and requirements for reporting serious adverse events had a greater impact on coordinator effort than internal billing requirements or the length of a study subject's visit. Therefore, a review of the 21 elements was performed and those items that were felt to have a high impact on complexity of effort were weighted (see Figure 2).

Figure 2: Example of Weighted Complexity Tool

Study Element	No Effort (0 points)	Minimal Effort (1 point)	Moderate Effort (2 points)	Maximum Effort (3 points)	Weight
Study Scope/Overall Complexity					
PI expertise and experience with clinical research- number of years and levels of experience the PI has.	N/A	Principal Investigator (PI) was lead on several trials and has a clear understanding of a PI responsibilities	PI has been Sub -I on a study (ies) and has enrolled and followed patients on a clinical trial	PI has none or minimal research experience and/or requires an increased level of engagement	1.6
Study Recruitment- estimated effort needed or complexity in subject recruitment activities.	N/A	Development of flyers or adding to LCD screens	Community outreach- Outside physician referrals	Specialized recruitment efforts will be required- Radio or TV ads, talks in the community	1.2
Target accrual- number of subjects planned to meet the study enrollment criteria and receive study treatment. Captured from budget for Mayo Clinic Florida target (if applicable).	0	<20	20 - 100	> 100	1.6
Eligibility Criteria- number of key requirements for subjects to participate in a clinical study. Consists of both inclusion and exclusion criteria.	N/A	1-10 eligibility criteria	11-20 eligibility criteria	> 21 eligibility criteria	1.6
Informed consent process (initial)- number of pages for informed consent. Does not include addendums.	No informed consent	1-10 pages	11-19 pages	> 20 pages	1.3
Screening procedures for eligibility- The number of procedures that need to take place after subject signs informed consent form prior to administration of treatment. Note: One lab draw with 5 studies would count as 1 procedure. If the subject will need to go to separate labs, this would be counted separately.	0	1-5	6-10	> 10	1.4
Screening visit (length)- Length of visit(s) required to determine subject eligibility for accrual.	N/A	< 4 hours	4-8 hours	Over 8 hours	1.4
Randomization/ Baseline Cycle 1 Procedures- Study procedures before the randomization visit can even occur (e.g. internal required registration, sending an eligibility packet to the sponsor, etc.)	0	1-4	5-9	> 9	1.4
Randomization/ Baseline Cycle 1 Length- time it takes for subject to complete visit where they receive their first study treatment.	N/A	< 4 hours	4-8 hours	Over 8 hours	1.4
Additional Personnel Needed- Personnel required outside of the core research team required to complete study procedures. Core research team is generally defined as the PI, CRC and Clinical Research Assistant.	N/A	Involves only the research team-PI, Study Coordinator and Clinical Research Assistant	Involves moderate number of different medical disciplines and staff-may include infusion unit, clinic nurses, genetic counselor etc./approx. 3 add'l teams	Involves high number of different medical disciplines and staff, requires more effort and coordination-may include involvement of hospital staff, overnight staff etc./approx. 4 add'l teams	1.4
Procedures needed after Baseline/ Randomization to End of Treatment (outside of treatment)- The average number of study procedures that occur at study visits during active treatment until the subject completes trial treatment. Note: each set of labs, EKGs etc. all count separately.	0	1-10	11-20	≥ 21	1.6

Scores were weighted by a multiplier ranging from 1.2 to 1.7 across all 21 items. Less complex or less time-consuming items were multiplied by 1.2 (e.g., type of study recruitment). The most complex and time-consuming items were multiplied by 1.7 (e.g., adverse event reporting).

From these weighted scores, the total possible score changed from 63 to a balanced and more relatable score of 100 points. This also allowed for a more intuitive breakdown of the high-, moderate-, and low-complexity categories across a 100-point spread.

Studies that were open to enrollment and new studies going forward, were assessed with the new weighted complexity score. This model has been implemented and sustained for the last two years.

Correlating Trial Complexity with Coordinator Capacity

Once a final version of the Complexity Tool was in place, the research leadership team in Mayo Clinic Florida aimed to use the complexity score as a baseline determinant of a clinical research coordinator's (CRC's) capacity. Various disease teams were reviewed; leadership chose examples of teams that appeared understaffed, adequately staffed, and overstaffed, to see if the "gut feeling" from the management team held true when the new scoring was applied.

As a small test of change, the leadership team selected three teams (disease pods) within the Cancer Clinical Research Office (CCRO) with their initial assumption that one disease pod was understaffed (gastrointestinal [GI] cancer), one was adequately staffed (breast cancer), and a third had capacity to take additional studies (leukemia). These three disease pods' scores were reviewed and a composite score per group was determined (see Figure 3). The score was then divided by the allocated CRC full-time employees (FTEs). After comparing the scores for the three sample disease pods, the leadership team identified a predictive score of 350 points as a potential target capacity score for a CRC.

Figure 3: Scores by Disease Pod within the CCRO			
	Breast Cancer Team*	GI Cancer Team**	Leukemia Team***
Total Team Score	1,197	938	789
FTE in the Team	3	2	3
Score per FTE	399	469	263
*Disease pod was adequately staffed for the workload			
**Disease pod was slightly understaffed			
***Disease pod was overstaffed or has capacity to take on additional studies			

From there, the remaining disease pods within the CCRO were scored. The leadership team then completed a stakeholder analysis and reviewed metrics with the CRCs, data coordinators, and PIs, to understand their level of understanding of the workload and what they felt was an ideal state or workload. Through these discussions, the team was able to finalize that the ideal workload for a CRC within the CCRO was a score of 375–400 points. Once a target workload score per coordinator was established, research leadership further engaged their PI community on campus to review the needs and existing resources of each disease pod.

Over the last three years, clinical trial activity on the Mayo Clinic Florida campus has tripled in volume and complexity. With finite space to add new staff, assessing capacity of the existing team, reallocating resources, and having meaningful discussions of closing non-recruiting studies have received increased levels of attention.

Through the use of the Complexity Tool and the creation of a “CRC Standard,” a maximum score per disease pod was able to be determined based upon their allotted FTEs. For example, if one assumes the maximum complexity score per CRC is 400, and GI cancer has two FTEs of coordinator support, the maximum score would be 800. When investigators were interested in opening new trials, the current pod score was reviewed to determine if there was capacity within the team to take on another study.

With the Complexity Tool, studies ranged generally from a score of 10–100. If there was adequate capacity (e.g., disease pod score of 600), the study was able to open without further review. If there was limited capacity available (e.g., disease pod score of 790), research leadership, in partnership with clinical department practice chairs, would review the disease pod’s portfolio of existing and in-development studies to determine if there were studies that were underperforming that could be closed, or if there were competing studies that would prohibit the proposed study. If no such situations occurred, the amount of additional required FTEs would be reviewed.

Before posting for a new hire, research leadership would review other disease pods that had capacity to determine if coverage could be attained within the clinical research unit. The research leadership team is currently in the process of implementing a model whereby teams that are at or near capacity, but that cannot financially support an additional full FTE, will be able to share a “floater CRC” resource with other teams. As portfolios grow, the existing floater CRC would become dedicated to a specific team when the need arises.

Linking Capacity to Budgeted Effort

The next step was to determine if the weighted complexity score could serve as a predictive measure of how much coordinator effort should be budgeted for a clinical trial. Research leadership retrospectively reviewed a sample of studies within the CCRO to document how much effort was originally indicated by the coordinator to complete study tasks versus the complexity score calculated (using the 100-point weighted scale).

Complexity scores for this subset of studies ranged from 25 to 81 and were categorized into three ranges: 25–45, 46–65, and 66–85. The average percentage of effort per a subject (without taking into account the number of visits) was 11%, 28%, and 40%, respectively (see Figure 4). We did not evaluate above 85 points for the retrospective review, as no studies had a score that high to include.

Figure 4: Predictive Measure		
Complexity Score (out of 100 possible points)	Complexity Level	Average % Effort for CRC
25–45 points	Low	11%
46–65 points	Moderate	28%
66–85 points	High	40%

When reviewing the amount of effort spent by the coordinator on the trials, rule sets were established based upon the complexity score. For example, in the CCRO, every study that had a complexity score greater than 55 utilized a minimum of 35% of coordinator time, with the majority of these studies being Phase I. By understanding the minimum amount of effort required for a trial, based upon the complexity score, we are now in a better position to develop more accurate study budgets and have precedent to draw upon to assist in the negotiation of per-patient amounts with trial sponsors.

Current State

Through this review, rule sets based upon the complexity score are now being established that will allow for a more solid foundation upon which the assumption of CRC time could be based. The leadership team is in the process of creating a mechanism through which feasibility could easily be determined based upon negotiability of a proposed budget. It will also allow for proactive conversations with the PI on studies that may require financial supplementation in order to support FTEs to open the study, and will create a standard that could be expanded to other roles, such as data coordinators.

Reference

1. Richie A, Gamble D, Tavlarides A, Griffin C. 2019. Trial complexity and coordinator capacity: the development of a complexity tool. *Clin Res* 33(5), 17–23. <https://acrpnnet.org/2019/05/14/trial-complexity-and-coordinator-capacity-the-development-of-a-complexity-tool/>

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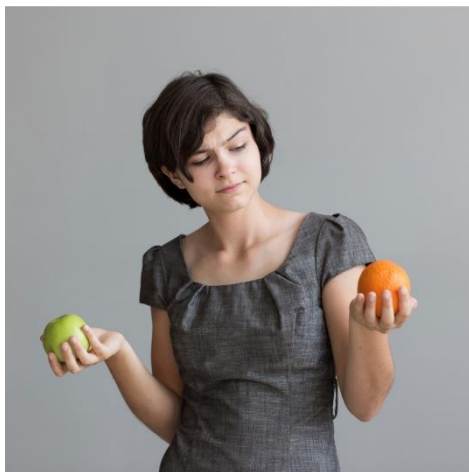
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PEER REVIEWED

Interventional or Non-Interventional? Analyzing the Differences Between Clinical Studies Using Medicines in the European Union

Tiago Silva, MSc; Alexandra Parnell, MSc; Christopher Bamford, PhD; Catherine Paulen, PharmD; Simona Francisconi, MSc; Jaclyn Bosco, PhD, MPH; Louise Parmenter, PhD, MSc



Clinical Trial Regulation (EU) No. 536/2014 (REG 536/2014),^{1} signed off on April 16, 2014, aims to simplify current rules, streamline trial application procedures, improve transparency, and harmonize clinical trial practice throughout all the Member States of the European Union (EU), in alignment with the tenets of the International Council for Harmonization (ICH) Good

Clinical Practice (GCP) guideline.^{2} This regulation has an extensive scope within clinical trials, covering authorization procedures, ethical considerations, implementation, operations, and disclosure, among other topics.

However, REG 536/2014 is not yet in force; currently, researchers rely on the Clinical Trial Directive (DIR 2001/20/EC),^{3} which merely provides the definitions and requirements Member States must adopt into their own local legislation. It is important to note that non-interventional studies are out of the scope of both the current DIR 2001/20/EC and the upcoming

REG 536/2014. As a result, there is significant variability in the classification of non-interventional studies across EU Member States with consequent impacts on their planning and execution on a multinational scale.

This paper aims to overview each type of clinical study referred to within the upcoming REG 536/2014 and analyze their impact upon the implementation of this Regulation, as well as the expected framework for non-interventional studies. For improved navigation, please refer to Table 1 for a list of abbreviations and acronyms used in this paper or otherwise tied to this topic.

Table 1: Useful Abbreviations and Acronyms

DIR 2001/20/EC	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
PASS	Post-authorization safety study
PRO	Patient-reported outcome
REG 536/2014	Clinical Trial Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Clinical Studies

Article 2 of REG 536/2014 defines a “clinical study” as any investigation in relation to humans intended a) to discover or verify the clinical, pharmacological, or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions to one or more medicinal products, or c) to study the absorption, distribution, metabolism, and excretion of one or more medicinal products, with the objective of ascertaining the safety and/or efficacy of those medicinal products.

This section further defines clinical studies as either “clinical trials,” “low-intervention clinical trials,” or “non-interventional studies.” Table 2 compares each clinical study type in terms of study objectives, methods, population, and regulatory/ethical requirements, in alignment with REG 536/2014.

Table 2: Comparison of Study Types

	Clinical trial	Low-intervention trial	Non-interventional study ^a
Objectives	<p>Pre-marketing: pharmacology, safety, and efficacy information for MAA.</p> <p>Post-marketing: to refine understanding of benefit/risk relationship under therapeutic use conditions and in accordance with the MAA.</p>	<p>Pre-marketing: pharmacology, safety and efficacy information for MAA, but IMP use is evidence-based and supported by published evidence.</p> <p>Post-marketing: to refine understanding of benefit/risk relationship under therapeutic use conditions and in accordance with the MAA.</p>	<p>Pre-marketing: not applicable.</p> <p>Post-marketing: to refine understanding of benefit/risk relationship under therapeutic use conditions, in accordance with the MAA and following normal clinical practice. {9}</p>

Methods	<p>Usually prospective, although there may be exceptions (case study 2 in Table 4).</p> <p>Treatments and procedures defined in the protocol.</p> <p>Monitoring and operations according to the ICH GCP guideline.</p>	<p>Usually prospective, although there may be exceptions (case study 2 in Table 4).</p> <p>Treatments and procedures defined in the protocol.</p> <p>Less stringent operations compared to other clinical trials.</p>	<p>Can be retrospective, cross-sectional, or prospective.</p> <p>Treatment and procedures follow clinical practice and cannot be imposed by the protocol.{3}</p> <p>Treatment prescription independent from study inclusion.{3}</p> <p>No harmonized European guidance or regulation for operational activities.</p>
Population	<p>Sample size depends on the study objectives.</p> <p>Usually stricter eligibility criteria.</p>	<p>Sample size depends on the study objectives. Sample sizes may be higher and eligibility criteria may be less strict than early-phase clinical trials.</p>	<p>Large sample sizes and heterogenous populations to reflect real-world conditions.</p> <p>Exclusion criteria usually compliant with the MAA.</p>
Ethical requirements	<p>EC favorable opinion.</p> <p>ICF mandatory.</p>	<p>Same as other clinical trials.</p>	<p>EC favorable opinion.</p> <p>ICF typically mandatory (may be waived under specific conditions).</p>
Regulatory requirements	<p>Competent authority(ies) authorization.</p> <p>Registration and disclosure in EudraCT.</p> <p>Country-specific regulations may require additional steps.</p>	<p>Same as other clinical trials.</p>	<p>Imposed PASSs: approval from PRAC (or local authority, if conducted in only one Member State).{9}</p> <p>PASSs: registration in the EU PAS.{9}</p> <p>Country-specific regulations may require additional steps.</p>

			Local authority consulting may be advisable to confirm non-interventional status.
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^a Non-interventional studies are not scoped in the REG 536/2014. This table presents guidance and requirements from other regulatory sources applicable to the European Union.

References: Directive 2001/20/EC, {3} Guideline on good pharmacovigilance practices Module VIII. {9}

Abbreviations: EC Ethics committee; EU PAS European Union Electronic Register of Post-Authorization Studies; EudraCT European Clinical Trials Database; GCP Good Clinical Practice, ICF Informed consent form; ICH International Council for Harmonization; IMP Investigational medicinal product; MAA Marketing authorization application; PASS Post-authorization safety study; PRAC Pharmacovigilance Risk Assessment Committee.

Clinical Trials

Article 2 of the REG 536/2014 defines a “clinical trial” as a clinical study whose treatment strategies, diagnostic assessments, and clinical monitoring procedures are determined and scheduled in advance by a clinical trial protocol, and do not fall within normal clinical practice.

Clinical trials are required before an investigational medicinal product (IMP) is authorized to be commercialized for the intended therapeutic indication(s). These trials collect pharmacological, safety, and efficacy information from human participants needed for marketing authorization. {4}

Clinical trials are also performed after marketing authorization is granted, to refine understanding of the benefit/risk relationship under real-world therapeutic use conditions. {4}

All clinical trials performed in the EU should receive authorization from the competent authority(ies) and be registered in the European Clinical Trials Database (EudraCT) prior to starting. {1,5} Country-specific regulations may require additional regulatory steps (e.g., approval of local data protection authorities or registration in local clinical trial databases). A favorable opinion from all applicable ethics committees (ECs) and an approved informed consent form are required. {1,6}

Low-Intervention Clinical Trials

The concept of “low-intervention clinical trial” is first introduced in the upcoming REG 536/2014 and is not part of the DIR 2001/20/EC. These trials use authorized drugs (excluding placebos) in accordance with the marketing authorization, or non-authorized drugs, if their use is evidence-based and supported by the published scientific evidence. These trials should not pose more than a minimal additional safety risk or burden to participants compared to normal clinical practice.{7}

As in all clinical trials, the assessment and treatment procedures of low-intervention clinical trials are to be determined by the protocol. However, less stringent requirements may be applicable. Specific conduct requirements should be based on a risk evaluation assessment to be performed for each trial.{7} Sponsors must be familiar with REG 536/2014, the European Commission guidance document describing Risk Proportionate Approaches in Clinical Trials, and applicable legislation of the target EU Member States to perform an appropriate risk evaluation and propose adequate conduct approaches. On the other hand, regulatory and ethical submission and authorization requirements for low-intervention clinical trials are the same as for other clinical trials.{1}

One potential concern regarding the introduction of the low-intervention trial concept is the lack of EU-consistent regulatory definition for “minimal additional safety risk or burden” in the upcoming REG 536/2014. As such, upon implementation of the new Regulation, there may be difficulties in defining a study that falls upon the borderline between a non-interventional and low-intervention definition. This can result in a single study being considered as non-

interventional in some Member States and as a clinical trial in others. Due to this situation, it can be difficult for sponsors to meet the study application requirements and compliance expectations.

To avoid such inconsistencies, the REG 536/2014 aims to provide a clear and harmonized definition for low-intervention clinical trials. To further reduce ambiguity, in June 2019, the European Commission issued the REG 536/2014 Draft Questions & Answers document, which has been frequently updated since that time (currently Version 2.3, dated November 2019, at time of writing).{8} Annex II of this document includes a decision tree aiming to establish whether a study is a clinical trial, a non-interventional study, or a low-intervention clinical trial, following some key aspects (i.e., whether the drug is an IMP, what effects is the study looking for and their purpose) (see Table 3).

Table 3: Decision Tree for Determining Study Type (Transcribed from Regulation [EU] No 536/2014 Draft Questions & Answers Version 2.3)

	A	B	C	D	E	F
A clinical trial of a medicinal product?					A non-interventional study?	A low-intervention clinical trial?
Is a medicinal product administered before or during the start of the clinical trial?	Is it a medicinal product?¹	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for these effects?	Is the product authorized in any EU Member State?
If a medicinal product is administered before the start of the clinical trial,	If you answer no to <u>all</u> the questions in column A, the activity is not a	If you answer yes to the question below in column B, the activity is not a clinical trial	If you answer no to <u>all</u> the questions in column C, the activity is not a clinical trial under the scope of	If you answer no to <u>all</u> the questions in column D, the activity is not a		

<p>and it falls under current practice, please go to column E.</p> <p>If a medicinal product is administered before the start of the clinical trial and it falls not under current practice, column E is excluded.</p> <p>If a medicinal product is administered after the start of the clinical trial, please go to column A.</p>	<p>clinical trial on a medicinal product.</p> <p>If you answer yes to any of the questions below, go to column B.</p>	<p>on a medicinal product.</p> <p>If you answer no to this question below, go to column C.</p>	<p>Regulation EU No 536/2014.</p> <p>If you answer yes to <u>any</u> of the questions below, go to column D.</p>	<p>clinical trial under the scope of Regulation EU No 536/2014.</p> <p>If you answer yes to <u>any</u> of the questions below, go to column E.</p>		
	<p>A.1. Is it a substanceⁱⁱ or combination of substances presented as having properties for treating or preventing disease in human beings?</p> <p>A.2. Does the substance function</p>	<p>B.1. Are you only administering any of the following substances?</p> <ul style="list-style-type: none"> • Human whole bloodⁱⁱⁱ; • Human blood cells; • Human plasma; 	<p>C.1. To discover or verify/compare its clinical effects?</p> <p>C.2. To discover or verify/compare its pharmacological effects? (e.g., pharmacodynamics)</p> <p>C.3. To identify or verify/compare its adverse reactions?</p>	<p>D.1. To ascertain or verify/compare the efficacy^{vi} of the medicine?</p> <p>D.2. To ascertain or verify/compare the safety of the medicine?</p>		

	<p>as a medicine? (i.e., can it be administered to human beings either with a view to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action; or with a view to making a medical diagnosis; or is it otherwise administered for a medicinal purpose?)</p> <p>A.3. Is it an active substance in a pharmaceutical form?</p>	<ul style="list-style-type: none"> • A food product^{iv} (including dietary supplements) not presented as a medicine; • A cosmetic product^v; • A medical device 	<p>C.4. To study or verify/compare its pharmacokinetics? (e.g., absorption, distribution, metabolism, or excretion)</p>			
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ⁱ Cf. Article 1(2) of Directive 2001/83/EC, as amended.

ⁱⁱ Substance is any matter irrespective of origin e.g. human, animal, vegetable, or chemical that is being administered to a human being.

ⁱⁱⁱ This does not include derivatives of human whole blood, human blood cells, and human plasma that involve a manufacturing process.

^{iv} Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.

^v The Cosmetic Directive 76/768/EC, as amended harmonizes the requirements for cosmetics in the European Community. A "cosmetic product" means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips, and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them, or protecting them in order to keep them in good condition, change their appearance, or correct body odors.

^{vi} Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing, or treating a disease and derives from EU pharmaceutical legislation.

References: REG 536/2014 Q&A Version 2.3 (transcribed from Annex II).{8}

Abbreviations: Q&A Questions & answers; REG Regulation.

However, these efforts toward harmonization may have an impact on the current standard practice. As an example, most Member States will currently allow post-authorization safety studies (PASSs; see next section for definition) utilizing patient-reported outcome (PRO) questionnaires to be run as non-interventional studies.^{9} Meanwhile, Article 2 of the REG 536/2014 provides that low-intervention clinical trials may include “additional diagnostic or monitoring procedures [that] do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.” Under this definition, it is possible that, upon implementation of the new Regulation, non-interventional studies using PROs not normally used in routine practice may be classified as low-intervention clinical trials, with regulatory requirements equivalent to a clinical trial. The impact of this attempt at harmonization remains to be seen.

Being only part of the upcoming REG 536/2014, the designation of low-intervention clinical trial is not yet in force in any EU Member State, with the exception of Spain, which adopted REG 536/2014 into local law in December 2015 (Real Decreto 1090/2015).^{10} In fact, some national authorities in some Member States have moved ahead with revisions to local regulations that deviate from the low-intervention clinical trial definition provided in the REG 536/2014. An example is the legislation released in France in 2016 (Code de la santé publique – Article L1121-1),^{11} following publication of the final EU Regulation text. The French law reorganized study classification into category 1, 2, and 3 research. While category 3 research remained harmonized with the definition of a non-interventional study provided in the current DIR 2001/20/EC, category 2 research is interventional research where the drug product is not the object of the research and where the intervention (i.e., a blood sample) poses minimal risk to patients. Any

low-intervention clinical trial involving a drug product would continue to fall under category 1 research, and is subject to full clinical trial requirements according to French regulations. Further modification of the law therefore appears necessary upon REG 536/2014 coming into force.

Non-Interventional Studies

Article 2 of DIR 2001/20/EC defines a “non-interventional study” as a study where the medical product(s) is (are) prescribed independent to inclusion of the participant in the study and as part of a therapeutic strategy, including diagnostic and monitoring procedures, which is not decided in advance by a study protocol but is applied according to the current clinical practice. As such, these studies seek to understand the use of a marketed product in real-world conditions, including risk/benefit, healthcare resource utilization, and patient/caregiver satisfaction, as examples.

Another example is the non-interventional PASS, a study carried out to obtain further information on a drug’s safety, or to measure the effectiveness of risk-management measures{9} (note: PASSs may also be designed as interventional studies, which require following the applicable clinical trials regulations).

In non-interventional studies, clinical procedures and assessments must follow normal clinical practice, as opposed to clinical trials, which follow the protocol. However, the definition of “normal clinical practice” may be subjective and prone to disagreement. For clarity and harmonization, the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP) Module VIII states that in non-interventional studies, “interviews, questionnaires, blood samples and participant follow-up may be performed as part of normal

clinical practice.” However, the application of such assessments should not be conducted in a way that is considered significantly different from clinical practice. {9}

Although defined in DIR 2001/20/EC, non-interventional studies are outside its scope. Due to the lack of harmonized regulation, some studies designed to be non-interventional may be considered clinical trials by EU authorities. The two blinded studies described in Table 4 were considered clinical trials in the EU for planning on collection of data to support the marketing authorization application of experimental IMPs, despite no IMP being given and normal clinical practice being kept during the study period. Sponsors are thus advised to consult with authorities when planning studies under these conditions and/or whenever the objectives or design may raise questions.

Table 4: Examples of Decisions and Rationale for Classifying Two Studies*

#	Study description	Authority decision and rationale
1	<ul style="list-style-type: none"> • Long-term safety follow-up of participants with Disease A, under normal clinical practice. • Participants previously exposed to experimental Drug A in a clinical trial for the management of Disease A. • Drug A had been stopped prior to study initiation. 	<p>Clinical trial</p> <ul style="list-style-type: none"> • Drug A was not authorized for Disease A at the time the long-term safety follow-up study was initiated. • Population was exposed to an investigational product under clinical trial conditions, as opposed to a real-world exposure. • Data collected in consequence of previous experimental exposure to Drug A and to support the marketing authorization of Drug A. • Rationale for this decision was subsequently supported by the REG 536/2014 Draft Q&A Version 2 document (question 1.15). {8}

2	<ul style="list-style-type: none"> • Use of previously collected blood samples in participants with Disease B to determine potential genetic markers. • Participants previously exposed to experimental Drug B in a clinical trial for the management of Disease B. • Blood samples aimed at correlating Disease B biomarkers with potential efficacy of Drug B. • Drug B had been stopped prior to study initiation. 	<p>Clinical trial</p> <ul style="list-style-type: none"> • Population was exposed to an investigational product under clinical trial conditions, as opposed to a real-world exposure. • Drug B did not have marketing authorization. • Despite no direct patient interaction, blood samples would be tested and results analyzed to support the marketing authorization of Drug B.
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*The examples in this table are of real clinical studies that have been blinded for confidentiality purposes. These were considered clinical trials by EU authorities, despite not involving exposure to an investigational product during the study period.

References: REG 536/2014 Q&A Version 2.{8}

Abbreviations: EU European Union; Q&A Questions & answers; REG Regulation.

Due to the lack of harmonized EU guidance or regulation regarding non-interventional studies’ operations and monitoring activities, sponsors and investigators must ensure the safety of study participants and the collection of high-quality data by following an appropriate study plan. Some EU regulations and guidelines should be followed for this purpose, including, but not limited to:

- Regulation 2016/679 on personal data protection.{12}
- Directive 2010/84/EU on pharmacovigilance and safety reporting (Article 107).{13}
- Directive 2001/83/EC on labelling requirements.{14}
- EMA GVP Module VIII, specific to PASS.{9}
- European Centers for Pharmacoepidemiology and Pharmacovigilance considerations on the definition of non-interventional trials.{15}
- Guidelines for good pharmacoepidemiology practice.{16}
- Applicable legislation and guidance issued by EU Member States.

There is no centralized submission procedure for non-interventional studies with the exception of non-interventional PASSs, imposed as an obligation by an EU competent authority.^{9} Because non-interventional studies do not have harmonized legislation, some Member States require submissions to regulatory authorities, while others do not. It is therefore important that sponsors are familiar with the regulatory framework of target EU Member States, and that they consult with local competent authorities and ethics committees (ECs) when justified.

Non-interventional studies generally do not require registration in an EU database, with the exception of non-interventional PASSs, which must be registered in the EU Electronic Register of Post-Authorization Studies.^{9} Nevertheless, some Member States may require registration in local databases, so sponsors should look to confirm this possibility.

As for ethical requirements, a favorable opinion of the central or local ECs (depending on local regulations) is required for all non-interventional studies, with the exception of Denmark.

Informed consent is typically required.

After implementation of the upcoming REG 536/2014, the aforementioned variability in local requirements across the EU is expected to continue as these studies do not enter the scope of this Regulation, being only defined as a “clinical study other than a clinical trial” (Article 2). This will not be problematic if all EU Member States are willing or able to update their local legislation to define non-interventional studies consistently across the EU. However, it is not clear that this will be the case.

The lack of a single, explicit regulatory definition for these studies can result in different interpretations from Member States when presented with the same study, with regulatory and operational consequences. If one Member State considers a study interventional, it will need to

follow all low-intervention clinical trial–specific requirements defined in REG 536/2014, substantially different from what is expected from a non-interventional study. As addressed earlier, this can be of special concern if a study falls upon the borderline between non-interventional and low-intervention definitions.

The European Authorities are conscious of the challenges that lie ahead. Within the currently available guidance on interpretation of the REG 536/2014{8} there are currently seven questions in the first section of the Q&A document related to the definitions of a low-intervention clinical trial and/or a non-interventional study. In addition, the frequency of updates being applied to this guidance document (four separate version updates between June and November 2019) indicates the importance of clarifying points such as these.

Based on this history, there can be hope that the European Commission will continue to provide clarifying guidance that sponsors and investigators can use to influence individual ECs and competent authorities within EU Member States if they face disharmonized opinions. However, in order to effectively plan a low-intervention clinical trial, it will remain important that all sponsor-related stakeholders are aware of the potential pitfalls that exist in relation to these definitions.

Conclusion

Upon implementation of REG 536/2014 in the EU, three different clinical study definitions are to be considered: clinical trial, low-intervention clinical trial, and non-interventional study.

Non-interventional studies are outside the scope of this Regulation, similar to the current DIR 2001/20/EC. With the lack of a harmonized EU regulatory definition for these studies, after the implementation of the new regulation it is expected that the variability in the classification of

non-interventional studies across EU Member States will continue. In addition, the implementation of a low-intervention clinical definition may lead to studies currently considered non-interventional to be considered clinical trials in the future, with operational and regulatory consequences.

Sponsors must be prepared not only for the upcoming EU Regulation, but also for how the Member States will adapt their own legislation after its implementation, as this will have potential impact in the clinical development of their products.

Disclaimer

The opinions expressed in this paper are the authors' own and not necessarily shared by their employer.

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SPECIAL FEATURE

Pre-Competitive Research Propels Modernization of Drug Development Using Modeling and Simulation

Rob Aspbury, PhD



It's hard to imagine that 37 leading, global biopharmaceutical companies would be willing to partner to develop a new technology and progress a scientific field, but that is exactly what the members of the Simcyp Consortium have achieved. Working together in a pre-competitive, collaborative research environment, the consortium's members are advancing physiologically based pharmacokinetic (PBPK) mechanistic modeling and simulation to predict pharmacokinetic/pharmacodynamic (PK/PD) outcomes in virtual patient populations.

Perhaps even more surprising is the fact that they have been successfully partnering like this for years. The Simcyp Consortium and the Simcyp® Simulator that it helps to develop have just celebrated their 20th anniversary.

The consortium's longevity is testament to the power of pre-competitive research. It allows pharmaceutical companies to pool resources and share knowledge in order to achieve a common scientific goal—before the need to pursue individual intellectual property rights and market exclusivity for a new drug become of paramount importance. In the case of PBPK modeling and simulation, its growing relevance in accelerating drug development, predicting safety issues, and

simulating drug performance in fragile patient populations has inspired advocates that include global regulators.

Expanding Simulator Use to Predict, Plan, or Avoid Clinical Studies

The Simcyp® Simulator employs *in silico* PBPK modeling and simulation to predict the fate of drugs in virtual populations. It combines *in vitro* data with *in vivo* absorption, distribution, metabolism, and excretion data and PK/PD outcomes to explore potential clinical issues in virtual populations before studies are conducted in patients. Employed to optimize clinical trials, evaluate new drug formulations, and conduct virtual bioequivalence studies, the simulator is applicable for both novel and generic drug development.

Some of the simulator's earliest uses, which remain among its most powerful, are determining the most appropriate first-in-human drug doses, identifying potential drug-drug interactions (DDIs), and understanding drug disposition in vulnerable populations—studies that for practical and ethical reasons are better conducted in virtual rather than real trial participants. In addition to being safer for the potential participants, this approach is faster and less expensive. The vulnerable populations in question include pregnant women, neonates and pediatric patients, and patients with complex diseases, co-morbidities, or reduced liver or kidney function.

Simcyp's whole body simulation approach can predict the PK/PD of small molecules, larger biologics, and antibody drug conjugates, which are a combination of the two. The simulator includes genetic, physiological, and epidemiological databases, which facilitate simulating virtual populations with different demographics and ethnicities.

The simulator also has organ-specific models, allowing it to simulate drug dispersion through the gut, different layers of the skin, the liver, the kidney, or specific compartments in the heart. Development of the dermal model was funded by a multi-year U.S. Food and Drug Administration (FDA) grant. On a similarly granular level, and to facilitate the development of tuberculosis (TB) drugs, Certara developed a population-based lung model that mimics drug disposition at different stages of TB infection. This project was partly supported by the Critical Path to TB Drug Regimen initiative.

The Simcyp Simulator is employed increasingly to inform drug label claims and, in some cases, can obviate the need for clinical trials. For example, the simulator has now been used to inform more than 60 novel New Drug Applications (NDAs) to the FDA, including more than 200 label claims made without the need for clinical trials. Those label additions include potential DDIs, dosing regimens, and data about new populations, including pediatrics.

Increasing Regulatory Acceptance

Working together, the Simcyp Consortium members have transformed PBPK modeling and simulation from a research concept into a technology that now forms an integral part of all phases of drug selection, development, and regulation. PBPK modeling and simulation has been adopted by all the leading regulatory agencies, including the FDA, the European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency, and China's National Medical Products Administration.

In 2016, PBPK modeling and simulation was featured in the FDA's Prescription Drug User Fee Act and Generic Drug User Fee Amendments, and many subsequent guidance documents. In addition, the EMA issued its First-in-human Dosing and PBPK/Modeling and Simulation guidance in late 2018.

This avalanche of new regulatory guidance encouraged even more rapid adoption of PBPK modeling and simulation.

Growing Industry Adoption

In September 2019, the FDA reported that pharmaceutical companies have been using PBPK modeling with new investigational agents for candidate selection in the preclinical phase; animal-to-human extrapolation studies; in DDI studies; in early formulation selection studies; to assess disease impact; and for dose adjustment for specific populations, such as those with organ impairment or for a pediatric population.

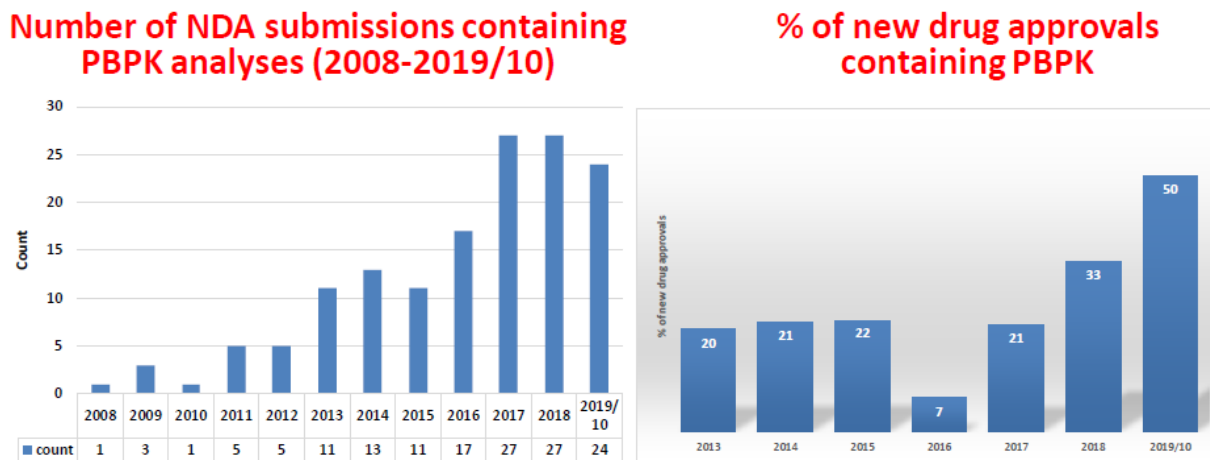
The agency also described several uses for PBPK modeling in generic drug development, including product-specific guidance development, such as alcohol dose dumping and risk

assessment for a change in drug release mechanism. This approach has also been used to demonstrate bioequivalence (BE), providing an *in silico* testing method in lieu of *in-vivo* BE studies for locally-acting drug products, or to extrapolate BE assessments in disease or age subpopulations.

For example, in June 2019, the Simcyp Simulator was used to demonstrate BE for the [first FDA approval of a complex generic drug](#) on the agency’s Abbreviated New Drug Application pathway. PBPK modeling can also be employed in drug product development to create a “safe space” to determine critical attributes of drug products, such as dissolution specifications.

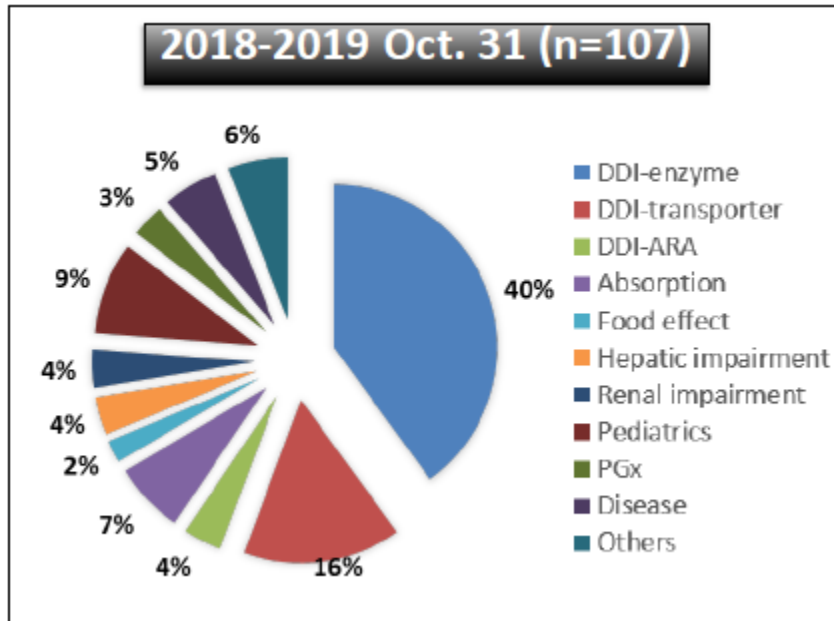
FDA further highlighted the dramatic increase in PBPK analyses included in NDA submissions and approvals between 2008 and October 2019 during its workshop on “Development of Best Practices in PBPK Modeling to Support Clinical Pharmacology Regulatory Decision-Making,” which was held in Silver Spring, Md. in November 2019. The Simcyp Simulator was used in most, if not all, NDA submissions listed in Figure 1.

Figure 1: NDA Submissions and Approvals Involving PBPK Analyses{1}



FDA also summarized the types of PBPK submissions received by its Office of Clinical Pharmacology from 2018 through October 2019 (see Figure 2).

Figure 2: PBPK-Related Submissions to FDA Office of Clinical Pharmacology{1}



Giving Back to the Community

The Simcyp Consortium is a global scientific endeavor and its members consider helping to advance modeling and simulation education to be part of their remit. The consortium presents two annual awards—the Most Informative Scientific Report and Most Effective Teaching Application Award—to recognize research excellence. Certara’s Simcyp Division Grant and Partnership Scheme also funds either a PhD or a postdoctoral research program every year.

In addition, Simcyp provides academic teaching and research licenses at no cost to more than 140 universities and research institutions around the world. Further, Simcyp publications (including articles, meeting abstracts, reviews, letters, and book chapters) have been cited more than 8,000 times.

Two decades on since its founding, Simcyp Consortium members continue to work together to determine the most important attributes to be included in the simulator’s annual update. Based on the voting of the consortium members, a set of “wish list” features are developed by the Simcyp science team. A new version of the Simcyp Simulator is released each year.

Creating New Consortia

The Simcyp Consortium has proven so successful that it has become the blueprint for other pre-competitive research consortia in the pharmaceutical industry. For example, Simcyp launched a Quantitative Systems Pharmacology (QSP) Immunogenicity (IG) Consortium, comprised of leading biopharmaceutical companies, in January 2017.

FDA defines immunogenicity as the propensity of the therapeutic protein product to generate immune responses to itself and to related proteins, or to induce immunologically related adverse clinical events (anti-drug antibodies or ADAs). An unavoidable consequence in biologics development, ADA binding may be manageable if parameters such as dose, frequency, route of administration, target patient population, tolerability strategy, or co-medications are optimized.

Finding the optimum for each drug requires a quantitative approach, hence the interest in QSP modeling. QSP combines computational modeling and experimental methods to examine the relationships between a drug, the biological system, and the disease process. By integrating quantitative drug data with knowledge of the drug's mechanism of action, QSP essentially bridges the gap between systems biology and pharmacometrics.

As a result of the consortium's work, a new technology for IG simulation is already demonstrating its ability to impact go/no go decisions. This could markedly improve Phase II success rates for compounds negatively affected by IG, a vexing problem for biologics drug developers.

Following the IG breakthrough, the company launched its second QSP pre-competitive Consortium—this time focused on immuno-oncology. Here, leading biopharmaceutical companies are partnering to develop a simulator that can model clinical populations of cancer patients and help to address the challenges of developing combination therapies. The large number and broad range of potential immuno-oncology therapy combinations cannot possibly be tested clinically. QSP simulation, incorporating the most current knowledge, is a viable method for combination analysis.

Conclusion

These industry-wide collaborations are enabling PBPK and QSP modeling and simulation advances to occur at a much faster rate than any one company could achieve alone. Sharing and utilization of pre-competitive information provide the opportunity to set industry-wide standards and practices, including publication of opinion papers, to influence regulatory thinking and future guidelines.

The growing knowledge base that is being created is also helping to ensure that patients receive the right medication at the most appropriate dose for them.

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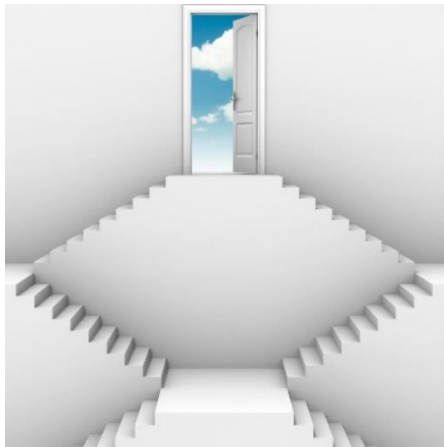


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SITE STRATEGIES

Six Sources of Influence to Evaluate in Your Research Training and Education Program

Cerdi Beltre; Geoffrey Schick, MBA, CHRC



When you oversee a clinical research program, a research site, or a health system, you take reputational risks if your research community is not well supported. Failure to provide appropriate access to training resources for each team member may be the product of inexperienced leadership at best, or irresponsible leadership at worst.

The mistake of not providing employees with adequate training, including access to resources and continuing education, can lead to low participant enrollment in clinical trials, protocol violations, and poor audit outcomes. This exposes a research site to reputational risk and possibly losing the trust of both participants and sponsors/contract research organizations (CROs).

Training programs present an opportunity to expand (or reinforce) core knowledge for all employees, but employers may find the investment hard to justify if they have tight budgets. Training often comes at the expense of work time that could be used to complete core responsibilities and projects, creating delays in employee deliverables. Contrary to these perceived drawbacks, training and development provide benefits for both the organization and the individuals that make them a worthwhile investment.

Employers who invest in their human capital via training and certification programs experience 218% greater income per employee than those who do not. They also experience 24% higher net income, which is a compelling argument for continued support for employee development initiatives, even during economic downturns. {1}

Having a framework for creating and evaluating a program to educate, train, and certify research teams helps to ensure its sustainability. Creating such a program often requires change, which can create a wave of resistance. To assess your program within a framework that helps to influence behavioral change, ask yourself questions adapted from the “Six Sources of Influence” from Kerry Patterson, et al. {2} An overview of this approach is also provided by J. Meier in his article on “The Six Sources of Influence Model — A Powerful Model for Change” {3} and summarized in Figure 1.

Figure 1: Six Sources of Influence

	Motivation	Ability
Personal	<p>1 Make the undesirable desirable</p>	<p>2 Surpass your limits</p>
Social	<p>3 Harness peer pressure</p>	<p>4 Find strength in numbers</p>
Structural	<p>5 Design rewards and demand accountability</p>	<p>6 Change the environment</p>

Let’s say—hypothetically—that you want to ensure your research organization consistently meets performance expectations related to enrollment and compliance. You know that having a certified coordinator on a study improves enrollment and compliance but have yet to achieve the

desired level of certification and training across your research site. In this hypothetical example, you have identified the necessary behaviors to achieve this:

- 1) Providing information and resources during start-up;
- 2) Granting access to well-trained and certified coordinators; and
- 3) Maintaining this certification via ongoing continuing education.

Below are the six sources of influence that you can evaluate to determine if you are supporting the vital behaviors needed to drive the desired outcomes and meet performance expectations.

1. **Personal Motivation:** Is everyone motivated to be trained/certified?

Personal motivation to be trained/certified may come from a desire to contribute to a higher purpose, such as being part of a team that brings new treatments to suffering patients. Perhaps, it comes from self-interest to obtain a promotion or greater responsibilities.

Whether or not an individual is motivated to receive training and education may depend on his or her intrinsic satisfaction; however, you can make the “undesirable” desirable by designing programs that clearly articulate value to the individual. For example, training on enrollment or research billing compliance could be considered boring but knowing that sponsors prefer sites with consistent compliance and enrollment performance across trials—and that poor performance can mean termination of the study at the site—may propel greater engagement.

The emotional commitment team members feel toward their individual and organizational goals is referred to as *employee engagement*. To be fully engaged, employees need to care about the organization and feel that the organization cares about their long-term success. Employers with a higher level of engaged workforce outperform their peers by a staggering 200+%.{4}

Programs that encourage and support training/certification demonstrate investment in their future. The outcomes are mutually beneficial, since the company experiences greater production

as the workforce continues to acquire new knowledge and skills. Remember, the millennial

generation is now the largest generation in the U.S. labor force, and an incredible 87% of millennials say that professional development, which can lead to career growth, is an important factor in their employment decisions. {5}

The outcome you seek: Make the undesirable desirable to personally motivate everyone.

2. **Personal Ability:** Is each person able to be trained/certified?

The ability to be trained/certified may require both aptitude and access. Consider for example that you hire a coordinator whose job description includes drawing blood, but during training it became clear that phlebotomy is a challenge for him or her. Can the coordinator overcome this limitation and be trained? Maybe not, if being too frightened by the sight of blood is the main challenge. Perhaps what is needed is deliberate practice during training to learn to draw blood.

Meanwhile, when attempting to remove limitations related to access to training, consider the time of day and venue that is most convenient for the teams. Is the ideal time before work, during lunch, or at another time? Should the meeting occur in person or remotely? Could you hold early morning, onsite meetings for different departments or sites to accommodate busy investigators who have clinical hours?

If you are unable to provide your team members with access to the training and education they need from within your research site, augment it with outside support via onsite or remote programs, webinars, conferences, and preparatory programs.

The outcome you seek: Surpass limitations to training/certification.

3. **Social Motivation:** Does your research environment encourage training/certification?

Research certification—such as via ACRP{6}—translates into higher enrollment, improved compliance, and better inspection performance. Can you invite team members to share examples of how their performance improved after training/certification, or can you publicly commend those that passed the certification exam? If so, this will not only make that person feel appreciated, it will help encourage others to do the same.

Team members may also want to learn about the career progression of someone who became certified and eventually held a leadership position. When you think of your research community, can you have team members share their experience to motivate others to do the same?

Investment in human capital through training and development will improve your research team's skills. These improvements turn out to be one of the greatest possible influences that an employer can have on increasing productivity. The National Center on the Educational Quality of the Workforce conducted a study that identified workforce education advances as being far more impactful on productivity than increases in the value of equipment. A 10% increased investment in education yielded productivity gains of 8.6% versus only 3.4% from equipment upgrades.^{7}

The outcome you seek: Harness the power of peer pressure to create the desire to become trained/certified.

4. **Social Ability:** Does your research environment enable staff to find help, information, and resources when needed?

Your research program is likely either maintained by several team members, or in larger institutions, by different departments (e.g., research compliance, institutional review board, research information technology, research finance, etc.). Each person conducting clinical trials should know exactly who to contact and/or where to go to access resources, including training and certification information.

Can you provide a site-specific operational handbook including easy-to-follow steps, expectations, and contacts? Do you have standard operating procedures for self-serve, introductory learning or tools for onboarding, with laminated cards reinforcing training/certification and noting who to contact and the required process? Can you establish a mentoring program to pair an experienced coordinator or investigator with a novice?

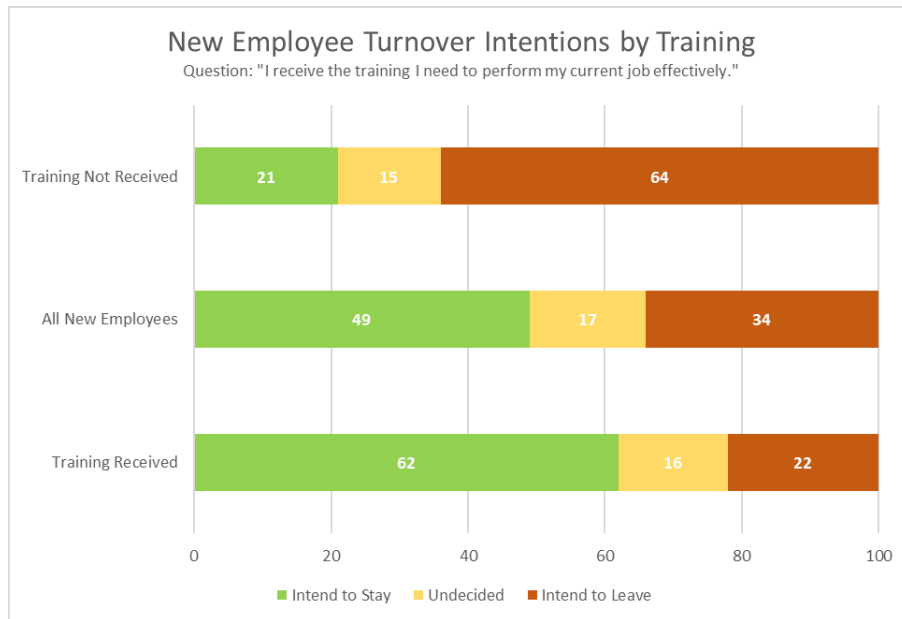
Generally, your team members want to do a good job. Top echelon research sites recognize that continued investment in the workforce not only leads to greater employee retention (see Figure 2 on study findings), but it is also more effective in increasing productivity. A full 40% of newly

hired employees will leave their position within the first year without the necessary job training, and two-thirds of the surveyed workforce feels training should continue throughout one’s career.{8}

Some organizations may choose to create a central office, a clinical research advisory group, or an executive committee to enlist champions across the institution who will back these programs. If you want your research organization to consistently meet performance expectations related to enrollment and compliance, the environment should support those goals.

The outcome you seek: People who can motivate, enable, or provide the help, information, or resources to sustain your program.

Figure 2: New Employee Turnover Intentions by Training



Source: "Study by the IBM Institute for Business Value—A New Way of Working" (2010)

5. Structural Motivation: Is your research organization encouraging training and certification?

For your research site to encourage training and certification, it must incorporate a system that includes both rewards and accountability. The motivation to provide research certification and

training for everyone within your research community may be driven by the desire to become known as an excellent research site.

Funding a certification award program centrally (within the clinical trials office, for example) could be an important step, as it removes the need to get buy-in at the individual site or department level. Can you provide bonuses for coordinators who pass a certification exam? Can you circulate a congratulatory e-mail for an individual who completes an important milestone (e.g., five years certified)? Are your job descriptions aligned with promoting certification and training?

Since certification could mean higher enrollment, improved compliance, and better inspection performance, encouraging this desired behavior by aligning rewards with it could prove cost effective.

The outcome you seek: Rewards and accountability that align with training and certification.

6. Structural Ability: Does your environment support training and certification?

Think of this as designing a program with the user's experience in mind. You have created a great program, but parking is impossible, the program begins at 6 a.m., the meeting room is cramped, and attendees do not have access to materials that they can print and review in advance. Does this sound as if you are enabling the expected outcome?

If you design the physical environment with the desired outcome in mind, participants are more likely to successfully engage in the training. For example, one healthcare system held quarterly study coordinator meetings across 19 hospitals, chose a central location for the meeting, then supported virtual attendance at four other locations where team members could join remotely.

Further, this healthcare system offered offsite continuing education during work hours, as the option was convenient and minimized distractions. It also provided web-based and learn-at-your-own pace training to support the institution's commitment to continued training and certification.

Do you allow time off or attendance at conferences to complete continuing education required for long-term certification? Can you clear calendars in advance to set aside times for certain training programs? Can you bring in experts to cover areas in which you lack expertise, such as research billing compliance or internal audits? The goal is to remove the impediments preventing participation in the desired training program.

The outcome you seek: An environment that makes it easy for your team members to obtain the necessary training and/or certification desired.

Conclusion

Implementing a training and certification program and using multiple sources of influence to sustain it can produce the organizational performance outcomes you desire. Ongoing evaluation will help to ensure that you stay the course and continue to reap the benefits of employee engagement, low turnover, increased productivity, and positive financial impact.

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RECRUITMENT & RETENTION

Harnessing Virtual Studies for Long-Term Follow-Up

Henry Anhalt, DO

In the world of diabetes, researchers have discovered that diabetes drugs have cardiovascular implications. The U.S. Food and Drug Administration (FDA) wants long-term follow-up studies to ensure safety—the virtual study model is perfect for that.



It was only a decade ago that the FDA issued guidance to ensure that new diabetes drugs were not associated with an unacceptable increase in cardiovascular risk. Given the high prevalence of cardiovascular disease in those with diabetes, there was a lack of understanding of how diabetes drugs contributed to major adverse cardiac events (MACEs).

Fast forward to now, and technology has ushered in methods that can help us gain a better understanding of how diabetes drugs impact the cardiovascular system in real-world settings. Chief among these new methods are virtual studies.

RCTs are Not Enough

As [research has shown](#), understanding how diabetes treatments work in the real world has significant importance for patients, providers, and beyond. Unfortunately, we cannot rely on traditional randomized controlled trials (RCTs) alone to yield this type of data, because their closely monitored—some would say artificial—conditions are not necessarily reflective of how patients use the treatments in real life.

One area where technology has been a boon for researchers and patients alike is in providing patient-reported outcomes that are more reflective of real-world conditions. Imagine having to remember episodes of low blood glucose levels for your next study phone call or annual physical. For many people, it's difficult enough remembering what was for dinner last Thursday. Luckily, some of the endpoints the FDA is looking for can be captured more predictably, and passively, with a wearable device or an app.

Digital technology has enabled the passive capture of metrics such as hours of sleep, heart rate, and physical activity; a device can automatically report these statistics as well as send patients reminders for medication times, scheduled telemedicine visits, etc. Thus, a virtual approach can capture a broader set of outcomes than traditional methods.

Virtual studies also amplify the convenience for patients, including the ability to provide electronic consent to participate in research and experience study visits from the comfort of home using telemedicine. The added convenience is often a key factor in patient retention; patients can go on with their lives without traveling to a research center potentially hundreds of miles away.

Reaching Out to Underrepresented Populations

Another driver for the healthcare community and the FDA is capturing data for the populations most affected by diabetes: communities of color. For example, Mexican-American and Puerto Rican communities have a diabetes prevalence rate that is twice that of their white counterparts, yet they [make up 4%](#) of diabetes study participants. African-Americans are [significantly more](#)

[likely](#) to have diabetes and [twice as likely to die from it](#) than whites, yet they remain underrepresented in research.

Moving care from the clinic to a patient’s home enables a more diverse group of people to participate in research—this is especially the case for diabetes, with its various comorbidities, which may make traveling to a clinic more difficult.

Conclusion

Virtual studies can unlock a trove of real-world data that can help determine how diabetes drugs affect the cardiovascular system over the long term. Researchers are able to capture more and different data points outside the confines of a tightly controlled RCT. The FDA wants this long-term follow-up data, and those in the virtual clinical trial space know that it can pave the way for more effective therapies and better patient outcomes.

With the aid of technology, virtual trials can provide the data that FDA is looking for at the same time as delivering better care to our patients.



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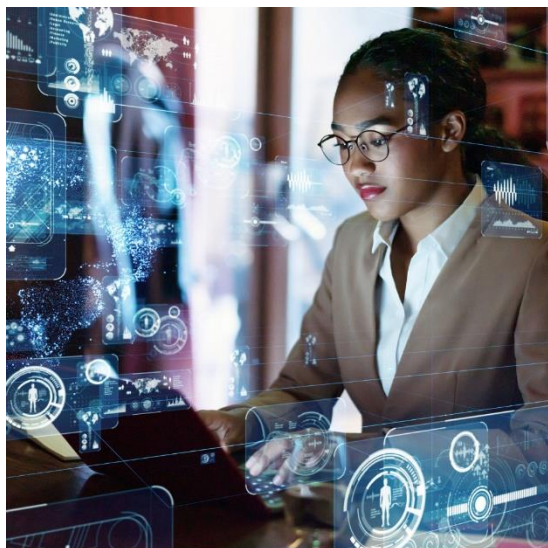
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SCIENCE & SOCIETY

Breaking Down the Silos: Creating Efficiency Through Connectivity and Privacy

Al O. Pacino

It has become vital to address the challenge of maintaining training and research competency levels of study staff for compliance purposes. The answer may exist in the building of a global, network-based infrastructure to fix the problem.



Whether you are involved in centralized or decentralized clinical trials, the expectations for keeping your site in regulatory compliance, while delivering efficient patient care, can be overwhelming for many clinical research professionals and associated managers. Governments and regulatory agencies are rapidly adopting already-established international regulations or developing modern privacy laws that require employers to verify and properly handle employee information by empowering healthcare professionals to own their information.

With the rapid evolution of privacy and international developments such as the European Union's General Data Protection Regulation (GDPR), many of the systems used to process professional information existing in silos become a risk and can result in major setbacks and liabilities for investigator sites. Innovation is necessary for mechanisms used to enhance training and competency levels globally, and to address the growing number of privacy regulations pertaining to protecting personal data.

Based on the needs of a specific region, having sites be more responsive to the demands of GDPR and providing for some of the universal requirements of site activities, including those tied to multiple therapeutic areas, are necessary when considering solutions. The key to tackling this issue is to provide reliable connectivity between stakeholders, including educators, accreditation groups, institutions, sponsors, and investigator sites.

By embracing a transnational collaborative model, clinical research competencies, training, education, certification, and experience records become more accessible to industry stakeholders, including patients.

Providing the Necessary, Globally Interconnected System

It's not uncommon to find individuals in a new city or town using applications on their smartphones to find restaurants, hotels, and a variety of other services. We must bring clinical research into the 21st century and organize industry service providers all in one place for the benefit of every industry professional.

By organizing industry providers into networking directories, site management and their staff can choose from services that align with their everyday managerial and compliance needs. An important component of the system can be registering and validating certified educators who deliver, distribute, and implement trainings, and it must track clinical trial competencies for study staff, as is currently required by regulatory agencies. To move our industry forward, it would be most beneficial to lean into the existing modern culture and interconnectivity of the different stakeholders.

The connection established between study staff and education providers does not have to exist on its own. Centralization of the records on training, certification, and other accomplishments of clinical research professionals would go together with a networks-based solution. Providing a live connection between internal departments can make the exchange and verification of healthcare professional experience, training certificates, and online courses easier to track and competencies easier to update in real time between departments.

The net result will be the increased promotion and tracking of career-building milestones tied to Good Clinical Practice, ethics/human subject protections, medical licenses, and the everyday work flow required for business and compliance within the context of a global industry that is now having to comply with GDPR and other privacy-focused demands.

Thinking Big is Paramount

An important aspect of modernizing our industry into an efficient network for improving study staff competency is the inclusion of new sites from across the globe—from those in developing nations to research-naïve hospitals and healthcare locations from more advanced countries. To make progress in any given therapeutic area, we must have a complete understanding of the clinical research ecosystem and broaden our understanding of non-Western world views.

From the perspective of those who advocate for more diversity in trial patients, a more connective infrastructure would facilitate and streamline patient education and standards of care while decreasing the risk of data variance as required by regulators. At the same time, a place would be provided within the network for certified translation businesses and nonprofits, in order to bridge the gap in competency internationally to maximize inter-rater reliability between countries.

The challenge to be taken up also involves patient screening instruments, scales of assessment, diagnostic tools, and competency and experience records, all of which should be shared in a more expedient, convenient, simple, and privacy-compliant system. The siloed, existing systems for completing compliance requirements has not gone far enough to handle the modern demands of time management for site and industry sustainability.

Conclusion

There is a growing desire for technology that enables frictionless sharing of data across the healthcare and clinical research ecosystem for driving faster, more cost-efficient methods of education and compliance for researchers across the globe. Developing an international infrastructure that equips investigative sites and industry stakeholders with broad connectivity, while providing the tools for long-term sustainability, will bring developed and undeveloped nations into a mutually beneficial relationship.

Let's take steps toward a world in which investing in the creation of connective business models minimizes the business risks while improving accountability between sites, educators, and institutions so that we are all in compliance with regulators, major privacy laws, and international requirements like GDPR. Using a global collaborative, interconnected system will empower research professionals to own their data while spending more time applying their knowledge to gain meaningful results and ultimately leave no patient behind.



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FORM & FUNCTION

Basket Clinical Trial Designs: The Key to Testing Innovative Therapies is Innovation in Study Design and Conduct

Lindsay McNair, MD, MPH, MSB



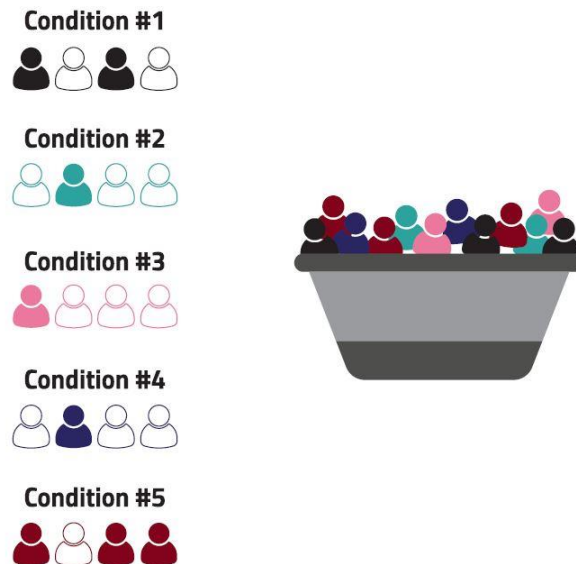
For many years, the randomized, parallel-group, double-blinded clinical trial was considered the optimal study design to assess the efficacy and safety of new investigational therapies. As the science behind therapeutic interventions has deepened and grown, the clinical trial designs through which those interventions can be best tested have evolved as well.

One of the therapeutic areas in which this has been seen most dramatically is oncology. “Precision medicine” includes the development of agents targeted to specific molecular profiles, including specific genetic mutations that may be driving cancer growth. These genetic mutations may appear in more than one type of cancer. For example, cancers with the TRK fusion protein may be found in the colon, breast, or lung. To study therapies directed against these specific abnormalities, it may make sense to include anyone with the target abnormality in the trial population, regardless of the location of their cancer.

Basket Clinical Trials

This is the premise of a “basket” trial design: that patients from different disease groups or subgroups, such as those with different types of cancer, are identified within those groups based on the presence of a specific factor. Patients with that factor who agree to be study participants are grouped together in one cohort, or “basket,” to receive an experimental product which is designed to work, or to work best, in that specific category of disease (see Figure 1).

Figure 1: A Visualization of the Basket Trial Design



Basket designs are intended to study a single investigational regimen in a number of different diseases or disease subtypes. The application of this idea is not just conceptual; the first drug to receive approval from the U.S. Food and Drug Administration (FDA) for a “tissue-agnostic” indication was pembrolizumab, for the treatment of specific patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, in 2018.^{1} Later that year, FDA approved larotrectinib for the treatment of solid tumors with a NTRK fusion mutation.^{2}

Basket trials are one of a set of novel clinical trial designs that are generally referred to as “master” protocol designs, which are intended to answer multiple questions in one study. Master protocol designs include platform trials (studies designed to assess multiple therapeutic agents in the same study population, amending the protocol design when the ongoing data interpretation indicates that either a futility or efficacy threshold is reached), and umbrella trials (looking at multiple investigational agents against the same disease as subgroups of one overall study population).{3}

As with all trial designs, each of the “master” designs has settings in which it may be optimally useful. Basket trial designs are often used as early studies in the development of a new agent. Although theoretically all tumors with the same mutation would respond in the same way to an agent targeted against the effect of that mutation, in practice that doesn’t always occur. Looking at patients with different types of cancer can help identify the most responsive tumor types, providing direction for future development.

In this way, the basket concept is not very different from the traditional early studies in which a new agent may be tested in a population that includes participants with “any solid tumor” and the goal of identifying early efficacy signals while collecting safety data. However, in the basket design the study population is enriched by including only those participants with markers that make them most likely to respond to the intervention.

While the basic concept of a basket trial is fairly simple, as with all conceptual study designs, the application in practice can become much more complex. In some studies, the agent being tested may have potential efficacy against more than one target mutation, so that there is more than one mutation-specific cohort, such as in the European Organization for the Research and Treatment of Cancer (EORTC) CREATE trial of crizotinib.{4}

Some authors report that the term “basket” has come to be applied fairly broadly to any study design in which a targeted therapy (or therapies) is being tested in a distinct disease subtype or types, but where the actual designs can vary from a single cohort of participants to what is effectively a series of distinct Phase II studies.{5}

While basket trial designs are almost exclusively discussed as oncology trials, because of the large number of oncology products that target specific molecular markers that lend themselves to this design, the general concept could certainly be applicable to other therapeutic areas as well. For example, an immuno-modulating agent could be tested in an early trial in participants who have a variety of auto-immune conditions rather than in one narrow indication.

Operational Considerations

In planning trials that employ a basket design, it's important to look at the operational implications, where the advent of master protocol designs has brought changes as well. These include the use of screening platforms to allow potential participants to be screened for multiple studies at the same time.

Further, the centralization of study governance committees and institutional review board oversight enables more efficient study conduct and streamlined communication and decision-making pathways. These are especially important factors when the studies may include adaptive elements that require real-time assessment of incoming information and rapid responses to those data.

However, despite the operational advances in some areas, master protocols may still be challenging to conduct. In most institutions, clinical divisions and administrative infrastructure are designed based on disease type or location: the breast oncology department, the gastrointestinal oncology department, etc. Research administration is often parallel to this, so that research team staffing, facilities, budgets, and other considerations are allocated and managed by disease-based divisions.

In disease-location agnostic study, this structure needs to be re-invented. Study coordinators may have to work together or to work across departments.

Summary

As therapeutic agents evolve and our understanding and ability to utilize precision medicine grows, the study designs that we use to test the safety and efficacy of these novel therapies must

evolve as well. While there is still a place for the standard randomized, parallel-group clinical trial, designs such as for basket trials allow the enrichment of study populations for specific markers to which therapies are targeted.

Taking advantage of both study design and operational advances in the way we conduct clinical research will help us to answer research questions with efficacy and scientific rigor, allowing us to identify promising therapies more quickly and to move them forward toward the clinic.

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