

APPLIED CLINICAL TRIALS

YOUR PEER-REVIEWED GUIDE TO GLOBAL CLINICAL TRIALS MANAGEMENT



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PROGRAM DESIGNS

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Debunking Six
eConsent Myths

All in Our Heads? The Power of Placebo Response



LISA HENDERSON
Editor-in-Chief

How often do you actually think of the mechanics behind a randomized clinical trial? For having a control group that receives a placebo vs. the group receiving the investigational compound? We know that in certain trials, for example, such as oncology, the randomized clinical trial doesn't mean these patients are getting a non-active placebo, but receive either a current treatment therapy or standard of care treatment.

For Duchenne muscular dystrophy, one family had two sons with the disease. One was able to enter a trial for a Sarepta Therapeutics drug, but the other child was too sick to receive it. In that case, the parents noted such marked positive response in receiving the treatment, they were anxiously awaiting that drug's subsequent approval so their other son could receive it.

That's not a true case of a placebo response in a randomized clinical trial, but a clear example of positive response on a drug.

In a recent webinar from Premier Research (<http://bit.ly/2q3FKRf>), it offered a comprehensive overview of placebo, with a specific focus in chronic pain trials. Webcast speakers referred to the etymology of the word placebo. Basically, a Latin word, which meant "to please." It received a negative connotation when, in later centuries, paid mourners attended funerals to sing the praises of the dead, without having known the person. They were called placebos, and, thus, people who deceived.

In clinical trials, placebos are designed to "deceive" both patients

and investigative staff to look the same as the investigational medicine. And randomization is a process to make sure that no one at the site level is sure who received the placebo or the active compound. Randomization and data privacy at this level is very complex, but there is more to placebo than placing people behind a data identifier. And this became clear in the webcast.

For example, patients with chronic pain are used to seeing one physician and form relationships with those physicians and their staff. In these cases, it's best that if a patient is in a study at the same center, they see different people and research staff. These staff will be trained to make sure all patients are evaluated in the same manner, that they adopt a very objective speaking style with the trial participant, and they received appropriate response training. The speakers called this "objective staffing."

The speakers also noted the placebo effect, by where the patient wants "to please" their doctor or staff by "giving" them the appropriate response. Conditions that are self-reported and subjective in their assessments are the most impacted by the placebo effect. As such, the objective training is essential in lowering the placebo response.

Another issue is sometimes, based on increased medical attention in a trial or by virtue of believing they are receiving an actual medication, people feel better.

Unfortunately, the placebo response has led to the failure of large clinical programs, with prior clinical efficacy, due to the inability to separate from a high placebo response. As sponsors work to address different options beyond opioids to manage pain therapies, clear strategies that address placebo response become very important.

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EU REPORT

THE COMMEDIA DELL'ARTE OF THE EMA RELOCATION

Relocating the European Medicines Agency (EMA) was always going to be hard—but no one ever expected it to degenerate into farce.

The shockwaves of that UK referendum, with its unintended consequence of obliging the agency to leave London, are still reverberating across the European Union nearly two years later—and not just because of the sheer administrative hassle, or because of the inevitable dip in the agency's performance. As of mid-March, the challenge had become all the more acute, with national rivalries turning the entire process into something akin to cheap theater.

Over recent weeks, festering resentment in Italy over Milan's failure to win the prize of hosting EMA has turned to fury as the winning candidate, Amsterdam, has had to resort to increasingly desperate improvisations to live up to its promise of a smooth transition. Not only did Amsterdam's bid already lack a suitable new building for the agency to move into on Brexit day, but it has had to re-invent its stop-gap solution because that, too, proved inadequate to meet the agency's needs even on a tempo-

rary basis. Milan is particularly aggravated because it was pipped at the post when the final decision was made not by a rational evaluation of the two rival bids, but by drawing one of the names out of a hat.

Milan's backers—even at the level of the Italian government—have pounced on the Dutch deficiencies to demand a re-think. Milan has an iconic building ready and waiting, they point out. And they are bolstering their case with arguments that the method for the final choice was so absurd as to invalidate the decision.

They have also marshalled their compatriots who sit in the European Parliament to mount a parallel campaign for a re-run of the contest, on the basis that the voice of MEPs was not adequately taken into account—rendering the procedure unconstitutional.

So with just over one year until Brexit, the future location of one of the EU's most-respected agencies is still clouded with doubt. At its best, there will be a frantic rush to move the agency into temporary office space (still being prepared) near Amsterdam's main rail station by the start of 2019, and then, nine months later, into the 15-story permanent office, on which, as of

last month, construction has not started yet. And the worst-case scenario is not that there will be some delay and slippage on those dates. It's that constitutional arguments may require a re-run (there are still at least two separate legal challenges now before the European Court of Justice, and the European Parliament and the EU Council of Ministers have still not signed off on the Amsterdam move).

Just as the European Parliament was about to vote on the issue in mid-March, a legal opinion from a leading academic expert on European law emerged claiming that the selection procedure is in breach of EU law.

If the stakes were not so high—in terms of the operations of the agency, and its contribution to European citizens' health—the situation might be considered comical. And it is impossible, in such circumstances, to not draw some parallels with the traditional stock characters of *Commedia dell'Arte*.

— Peter O'Donnell



NEWS NOTES

LEADING CROs FORM NEW INDUSTRY STANDARDS GROUP

Six contract research organizations (CROs) and Veeva Systems have introduced Align Clinical CRO, a new industry standards group dedicated to making it easier for sponsors and CROs to work together during clinical trials. Founding members, with input across the industry, plan to help create open technology standards intended to help increase sponsor and CRO productivity, reduce operational costs, and run trials faster.

For the first time, CROs, including ICON plc, Medpace, Pharmaceutical Product Development (PPD), PRA Health Sciences, Syneos Health, and UBC are coming together to de-

velop open technology standards to transform clinical trial operations across the entire industry to speed product development.

Report: Alz biomarkers will be key

According to the recently released Alzheimer's Association 2018 Alzheimer's Disease Facts and Figures report, the identification of biomarkers for Alzheimer's disease will be critical to improving disease diagnosis and researching treatments that may prevent or delay the onset of clinical symptoms, such as memory loss, confusion, and difficulties carrying out routine day-to-day tasks. The report highlights new economic modeling data showing early diagnosis during the MCI stage

of the disease would result in cost savings as much as \$7.9 trillion over the lifetime of all Americans living today.

Celgene, Prothena ink R&D pact

Prothena Corporation plc, a late-stage clinical biotech focused in the neuroscience and orphan categories, has entered into a global collaboration with Celgene through a subsidiary, to develop new therapies for a broad range of neurodegenerative diseases. The multi-year deal is focused on three proteins implicated in the pathogenesis of several neurodegenerative diseases, including tau, TDP-43, and an undisclosed target.

— Wire reports

WASHINGTON REPORT

THE PULL AND TUG ON ORPHAN DRUG DEVELOPMENT

FDA has been working overtime to streamline and accelerate research and approval of therapies to treat rare diseases, many life-threatening and affecting children. Last year was a record year for orphan drugs, as FDA approved 77 therapies with new orphan indications and granted 476 orphan drug designation requests. Since the landmark orphan drug program was established in 1983, FDA has approved more than 650 therapies for rare diseases, and more medical devices for orphan conditions are emerging. FDA's accelerated approval and breakthrough therapy initiatives further encourage R&D on rare disorders.

At the same time, the high cost of many orphan drugs and concerns about biopharma companies gaming exclusivity policies to limit competition has undermined public support for incentives driving rare disease research. These tensions were apparent as Congress moved to eliminate the orphan drug tax credit as part of the Trump administration's broader tax reform legislation enacted in December 2017. The policy permits sponsors to deduct from taxes half the cost of conducting clinical trials for therapies designated by FDA as orphan drugs. The final tax bill softened the proposed cutback to allow continued deduction of 25% of research costs. But Jim Greenwood, CEO of the Biotechnology Innovation Organization, predicted that the change will make it harder for small biotech companies to raise the funds needed to develop therapies for small patient populations.

Further Congressional proposals raise additional challenges. There is talk of narrowing an exemption for rare disease therapies from the 340B drug pricing program, which permits orphan drugmakers to avoid extra discounts to certain hospitals and providers. Policymakers question whether orphan drug

tax credits and added exclusivity should be awarded to firms repurposing older, common drugs with a secondary indication for a rare condition. Similar concerns have emerged over benefits for drugs initially approved as orphans that subsequently gain wider uses. FDA took action last December to close a loophole allowing companies to avoid pediatric testing requirements when developing a widely used drug to treat a rare pediatric condition.

Faster designations

Meanwhile, FDA is working with biopharma companies and patient groups to bring more rare disease remedies to market. An early initiative by FDA Commissioner Scott Gottlieb was to update the agency's process for assessing orphan designation requests from sponsors. FDA's Office of Orphan Product Development (OOPD) faced a backlog of some 200 requests due to steady increases in such submissions—568 designation requests in 2016, and more than 700 last year. An FDA action plan issued in June 2017 helped clear up the backlog and established a 90-day timeframe for processing new designation requests. In February, FDA announced further actions to make it easier and faster for sponsors to submit designation requests and for FDA to review them.

More efficient R&D may come from proposals for innovative clinical trial designs with more meaningful endpoints and greater use of real-world evidence in orphan drug development. FDA and sponsors are working with patient advocacy groups to better define endpoints and study inclusion criteria and to obtain patient preference information, experience data, and patient-reported outcomes from clinical studies. A draft guidance issued by FDA in December 2017 encourages

sponsors of rare pediatric disease therapies to join multi-drug, multi-arm trails to reduce the number of children needed to test new therapies for U.S. and foreign markets.

A related strategy is to establish natural history models of rare diseases to reduce the need for placebo arms in small studies, where patient recruiting is particularly difficult. FDA and the National Institutes of Health funded six natural history studies last year, and FDA's Gottlieb plans to use some of a budget increase for 2019 to support clinical trial networks able to enhance understanding of the natural history and clinical outcomes of rare diseases.

FDA also announced in February a collaboration with the National Organization for Rare Disorders (NORD) on initiatives to further incorporate patient experience into clinical trial design and development programs. A public workshop in May will address how FDA should evaluate orphan drug designation requests for molecularly defined diseases, noting that tissue agnostic therapies that target a cancer tumor's genetic features, rather than tumors in specific body organs, may alter the definition of "disease" and the appropriate application of orphan drug incentives.

These initiatives won't completely quiet the debate on the regulatory framework and role of incentives in spurring rare disease research. Recent analysis indicates that many orphan drugs are approved for market much faster than non-orphan therapies. That raises questions about whether to continue basing the orphan designation on treatments for less than 200,000 patients, or to vary that standard to reflect potential for a new rare disease treatment to gain broader uses in the future.



— Jill Wechsler

FDA NOTES

The FDA recently released the following industry guidance documents:

3/26/18: Chronic Obstructive Pulmonary Disease: Use of the St. George's Respira-

tory Questionnaire as a PRO Assessment Tool Guidance for Industry

2/28/18: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

2/15/18: Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older (draft)

CISCRP CORNER

PATIENT INPUT INTO LEVERAGING THE HEALTHCARE PROFESSIONAL'S ROLE

This article is the second in a series on the results from the Center for Information and Study on Clinical Research Participation's (CISCRP) 2017 Perceptions & Insights Study. Nearly 12,500 people worldwide responded—including the public, patients, and study volunteers—and provided valuable insights into opportunities to improve global education, outreach, and engagement.

Conversation starters

While almost three quarters (71%) of people worldwide who have never participated in a clinical trial indicate they would be willing to do so, 90% indicate that they have never been asked by their doctor. Among individuals managing a disease, less than 25% have had their doctor or nurse suggest a trial as a treatment option.

In this article, we explore patient perceptions on the importance of the healthcare professional's (HCP) role in providing support and reliable information in the search for a clinical trial, and highlight new opportunities for increased patient enrollment.

Currently, those without clinical trial experience indicate that they would most likely begin a search for a clinical trial by asking their own HCP (61%). It should be noted that respondents from Europe were somewhat less likely to do so (54%) when compared to other regions. An online clinical trial registry was also mentioned as a starting point, particularly among those who had previously participated in a clinical trial (50%) who were more likely to use the resource than those who had no prior clinical research experience (38%). A general online search was also frequently mentioned among those who had never participated (31%), with 18-to-34 year olds the most likely (46%) to begin looking for a clinical trial on a search engine such as Google or Yahoo.

The public reports referring to a variety of sources that could be unreliable or that may lack helpful information that would be useful to know when making a decision to participate. This could contribute to the lack of confidence the public reports feeling in their

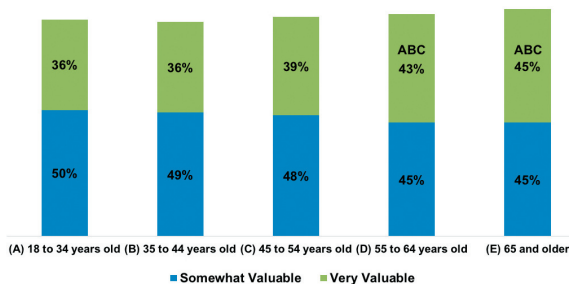
ability to identify clinical trials appropriate for them.

When asked how patients should best learn about clinical research, 64% of non-participants chose their HCP, and additionally felt it was important for their HCP to be aware of clinical trials in their communities (94%). Furthermore, the majority (88%) would find it valuable to learn about study options during a regular doctor visit, with older populations finding this the most valuable (see chart). Yet, 73% of respondents claimed that they never or seldom discussed a clinical trial as a treatment option with their HCP, with respondents from North America, Europe, and Asia-Pacific the most likely to have never discussed study options with their doctor. In contrast, South Americans considered clinical trials as a treatment option during doctor visits the most (59%), and were the most likely to report feeling "Very confident" about finding a clinical trial that is right for them (25%), illustrating the significance of a trusted physician's involvement in identifying a clinical trial to participate in.

The "so what?"

Patients' desire to turn to and consult their HCP about participating in clinical trials highlights opportunities for increased enrollment. According to a recent study by the Tufts Center for the Study of Drug Development, the majority of physicians in an online survey (91%) feel comfortable discussing clinical trials as a treatment option with patients, but lack access to trial information (54%), are unsure of where to refer patients (48%), or do not have enough time to learn about the trial (33%). To increase public confidence in finding an appropriate clinical trial and likelihood of HCPs recommending clinical trials as treatment options, pharmaceutical companies should more actively approach doctors well

How valuable do you feel it is to be presented with clinical research study options by your primary care physician (general practitioner) or specialist during your regular doctor visit?



Source: CISCRP Perceptions & Insights Study 2017

Sample Size: N=10,233. Respondents indicating "never participated in a clinical trial"

Letters indicate statistical significance at 95%

in advance of the enrollment phase. By providing HCPs with ample information about the clinical trial and sufficient time to review, pharma companies can leverage the trusting relationship between doctors and their patients and effectively connect more people to clinical trials right for them.

— CISCRP Research Services: Nova Getz, Annick Anderson, Jasmine Benger

Study methodology

The objectives of this study are to establish routine global assessments of public and patient perceptions, motivations, and experiences with clinical research participation to monitor trends and identify opportunities to better inform and engage the public and patients as stakeholders and partners in the clinical research enterprise.

Between May and July 2017, CISCRP conducted an online international survey. The survey instrument was based in part on questions posed in past surveys. CISCRP received input and support from pharmaceutical, biotechnology, and contract research organizations (CROs), and from investigative sites. A total of 12,427 respondents completed the survey. The online questionnaire was reviewed by an ethical review committee. CISCRP collaborated with Acurian, Clariness, CureClick, HealthUnlocked, and Quintiles to reach and engage respondents.

For more information about CISCRP's 2017 Perceptions & Insights Study and to download reports, visit www.ciscrp.org.



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With the cost of drug development now exceeding \$2.5 billion, the selection of molecules with the highest potential for success is crucial. Access to patient populations, Principal Investigators and sites is imperative as they are all finite and the demands placed upon them continue to increase.

With a global network of Early Clinical Development (ECD) sites with proven therapeutic expertise and access to diverse patient populations, you can improve the outcome of your early phase development efforts and move healthcare forward.

Hear about a proven approach to ECD using a network model to optimize your efforts and get you to proof-of-concept earlier. Whether you need normal healthy volunteers (NHV), diverse patient groups, or you're using hybrid designs (NHV + patients), attend this webinar to understand how this approach can provide the right sites, patients and expertise to positively impact the speed and cost of your early phase development.

Key take-aways:

Execute your Early Clinical Development trials with new levels of efficiency and effectiveness for your Phase I and early proof-of-concept studies:

- Use a global network of sites for targeted recruitment of NHV and access to diverse patient populations in geographical regions
- Leverage established relationships to streamline contracting and site budget negotiations for faster site start-up
- Work through a single, dedicated partner with therapeutic and operational expertise for cost-effective and streamlined delivery of healthy volunteer, patient or hybrid studies

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Q&A

LILLY JOINS FORCE ON CLINICAL TRIAL PATIENT EDUCATION

Patient engagement is a popular topic and is becoming more specific, as industry leaders make their mark on changing the way we run clinical trials. Of recent, several non-profit initiatives, such as CISCRP and One Person Closer, are promoting clinical trial education with patients. At ExL's CROWN Congress earlier this year, Kevin Hudziak, innovation lead at Eli Lilly, discussed how the big pharma is changing the face of clinical trials through patient engagement and education initiatives.

Q: The concept of patient engagement is changing. What does patient engagement mean to you?

HUDZIAK: Patient engagement is a process of actively listening and engaging with patients to better understand their healthcare journeys. Patient engagement must be an ongoing process to develop a relationship of honesty and trust. Lilly must focus on the value of patient input to help us design clinical trials that fit better into patients' lives. We also need to engage more effectively with caregivers and understand their perspectives, as they are critical to supporting the patient on their journey. It is important to point out that new medicines are not possible without the volunteers that participate in trials as well as the physicians and staff that conduct clinical trials. Therefore, it is imperative to involve those individuals more proactively in clinical trial design and execution.

Q: How are patient behaviors changing?

HUDZIAK: Patients and patient communities/advocates are becoming empowered to take a more active role in healthcare, and the digital world is altering the way that people seek healthcare information. Patients are also self-identifying for clinical trials. They are educated and knowledgeable about treatment options. All of these characteristics combined mean that we must adjust effectively to the critical role patients can play in transforming clinical trials in an ever-evolving future state.

Patient awareness of clinical trials has traditionally been quite low, so we need to find ways to actively educate them and provide online resources as they seek options in the

digital world, to help them gather information to support the decision that is best for them.

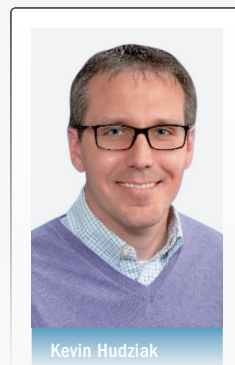
Q: How is Lilly adapting to those changes?

HUDZIAK: Lilly has responded to the empowered patient in several ways.

1. We have developed a website called Lilly TrialGuide to help educate and raise awareness for clinical trials as a healthcare option. On the website, we provide patient-focused content using health literacy principles to ensure that patients can more easily consume and understand the complex information, including therapeutic area specific websites for oncology and Alzheimer's disease. We have also focused on using storytelling as a critical tool in providing and sharing content that is relevant to patients. As a couple of examples, we are sharing caregiver stories and helping to raise awareness of clinical trials via the Hero's Journey Art Project.

2. Across the industry, we know that we need to shift the model from one where we bring the patient to the trial to bringing the trial to the patient, fitting the trial within the schedule and the life of patients to make it as convenient as possible. We cannot expect the patient's caregivers to take, say, six hours of their lives for a visit and occasionally drive them to and/or from the visit. Lilly continues to explore many initiatives around how to conduct trials more remotely, especially when it comes to implementing traditional procedures, such as blood pressure measurements and blood draws. We are trying to develop models where we may be able to do this from a local pharmacy or a local doctor's office; pharmacies can share the information without making the patients travel 1-2 hours to a study site. There are several initiatives within pharma that look at ways to make a trial more remote. For example, sending the study drug or a device directly to the patient at their home. These initiatives are changing the way that not only patients, but also families and caregivers, can help. However, the timing for when this would become a reality is still uncertain.

3. The most important innovation has not necessarily been technology or websites, but simply talking with patients to better understand their needs. The personal interaction with patients has been a key driver of innova-



tion. Lilly built a Clinical Innovation team with experts from across the pharma industry to think differently and develop solutions to aid patients and caregivers in the decision-making process. For example, we have an active Twitter feed @LillyTrials that allows us to engage with patients and caregivers via tweets and tweet chats.

Q: How's Lilly improving the connection between patients and sites?

HUDZIAK: A key component of Lilly TrialGuide is connecting patients to research centers conducting Lilly trials. If potential patients locate a promising clinical trial on the website, they can connect with sites directly by navigating to the site contact information on Lilly TrialGuide via the "Connect to Study Center" option. If a patient or caregiver can't find a trial specific to their needs, we have also created an optional service on Lilly TrialGuide called "Alert Me" that allows site users to sign up to receive email alerts if a trial is added in the future that fits a set of criteria that the user creates in a profile.

We also develop study-specific patient recruitment websites that contain more specific information on individual clinical trials that are actively recruiting. We use digital outreach to help identify potential patients and connect them to the website. The website will often have a simple pre-screener to help them understand if the trial may be right for them. If they pass the pre-screener, the patient can then share their pre-screener results with a clinical trial site near them. Additionally, we are piloting some new concepts to help connect patients to study sites on a couple of clinical trials.

— Moe Alsumidaie is Chief Data Scientist at Annex Clinical and a regular contributor to Applied Clinical Trials



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The signals are clear. We are in a period of intense innovation in immuno-oncology. In 2017 the FDA approved 45 novel immuno-oncology drugs – more than double from 2016. Among these approvals were two CAR-T (chimeric antigen T-cell receptor) products, and several drugs that inhibit immune “checkpoints.” Both represented new, powerful treatment options for cancer patients worldwide.

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Barriers and Solutions to Smart Clinical Program Designs

Mary Banach, Hon-Sum Ko, Steven Hirschfeld, Maria Benjegård, Ian Fisher, Mitra Rocca, Rashedul Hasan, Kerstin Forsberg, Dale Plummer, Courtland E. Yockey, Johann Proeve, Laszlo Vasko

How the Clinical Development Design (CDD) Framework can offer repeatable, reusable clinical designs based on “enabling information.”



PEER REVIEW

Due to ever increasing expenditures and difficulties associated with successful development and launch of innovative new medical products, the pharmaceutical industry has devoted substantial effort to root cause analyses.^{1,2,3} Taken together, these analyses show increasing complexity of clinical development with concomitant significant risks to the return on R&D Development investment.⁴ Furthermore, efforts to streamline clinical development processes with automation and digitization of data capture and reporting have failed to improve overall product approval rates or lower the cost of clinical research.⁵ The seeming paradox of process improvement without concomitant positive impacts on clinical development outcome led to the formation of a collaborative team in 2013 within the European Federation of Pharmaceutical Industries and Associations (EFPIA) called “Smart Program Design.” The Smart Program Design team published an article in 2015, “Smart Program Design through a Common Information Model,” which proposed improvements to the standard clinical program design approach involving precompetitive collaboration and information sharing.⁶ The group identified four key challenges to consistent and repeated smart clinical program designs:

1. Design information is captured ad hoc.
2. There is an inability to learn from past programs, both within organizations and externally.
3. Current industry information standards do not cover program level or the rationale behind these designs.
4. There is limited opportunity for progress in future opportunities in improving clinical program⁶

Thus, a gap exists for a common information model to describe the key building blocks essential in representing a clinical program and the corresponding design rationale, which allows for organization of information for reuse, facilitation of communication, and enablement of innovation. The common model should bridge between data and decision, and between decision and target product profile (TPP).⁶

A presentation of these concepts at the 2014 Clinical Data Interchange Standards Consortium (CDISC) IntraChange conference resulted in a recommendation by Wayne Kubick, chief technical officer (CTO) of Health Level Seven International (HL7) and former CTO of CDISC, to initiate work on a broader set of information standards to address clinical development program design, including the capture of design decisions, rationale, and references.

Current data standards focus on describing and capturing the clinical trial protocol and data rather than the design process. No data standards that apply to research operations or their related critical decision-making process exist. Hence, we took advantage of an opportunity in the Pharmaceutical Users Software Exchange (PhUSE) Semantic Technology group to develop the Clinical Development Design (CDD) Framework.

The purpose of the CDD Framework is to apply the principles and process of a design-based approach to the development program for a medical product, with emphasis on the identification, collection, and use of relevant information in a structured manner. This will enable decision-making and construct a learning system framework that facilitates ongoing improvement and efficiency.

The model is based on the principle that decision-making is dependent on and enhanced by what is termed

“enabling information.” In this model, the capture and use of enabling information is based on design principles.

Overview of design decisions

Our first question was how are design decisions made in other industries? Other domains with ongoing dynamic decision-making can inform clinical research program development. In *Thinking: Fast and Slow*, Daniel Kahneman explores decision-making.⁷ He stresses that each industry needs ways to ensure the product’s quality from initial design through production and final inspection. In each stage, we are framing the problems that need to be solved and the corresponding decisions that need to be made. He suggests that at each of these stages—design, production, and final inspection—we look for ways to improve our design decisions in order to improve our product. Kahneman also stresses the concept of “noise” or lack of reproducibility, the variability in design decisions.⁸ He recommends ways to decrease the noise in design decisions by building algorithms, rather than depending solely on individual human judgment.

Overcoming human inconsistency as a solution to better decision making is supported by the work of Theresa Winhusen.⁹ She focuses on the pre-implementation phase of multi-site pharmacological clinical trials and details the causes of delays and how they affect the study. The three primary causes for delays in the pre-implementation period are: (1) unforeseeable events, (2) underestimation of how long a project will take, and (3) difficulties in coordination of the many parties involved in the clinical trial. She proposes that with the proper tools, the impact of these types of delays can be overcome.

Roger Buehler, consistent with Winhusen and Kahneman, shows examples of planning fallacies found in a wide range of industries, and presents tools that can assist in more accurately planning a project.¹⁰

While incorporating algorithms and tools into the decision-making process is advantageous to improve consistency and precision, the tools must be applied to sufficient and accurate information to be effective. K.M. Sutcliffe notes that too little as well as too much information can be difficult for a manager to interpret and apply to successfully manage a project.¹¹ Dan Lovallo and Kahneman show how managers need the subjectivity removed from the design decisions to put out a more accurate estimation of the success of the product.¹² Kahneman suggests managers and decision-makers can reduce noise and improve consistency by employing filters.⁸ Sheehan, Hirschfeld, Foster et al. point out that another way to reduce the noise is to use a set of common data elements (CDE) to obtain a more accurate signal.¹³

Describing design decisions in CDD

High quality design is most commonly manifested by success in the creation, development, commercialization, and optimization of a tangible product with a specified use, such as a car, a house, or a software application. While product users make multiple decisions during its use, the product is typically not changed on a daily basis. Design in the realm of clinical research is different, however, in that the research can be reevaluated and adjusted continuously. Clinical research on a medical product is dependent on the process of creation, development, and optimization of a scientifically robust, operationally feasible, and eco-

nomically relevant research program to generate compelling evidence for internal decision-making, regulatory evaluation, and public confidence in its efficacy, safety, and cost-effectiveness. In contrast to the mass manufacture of consumer products, each clinical development program for every biomedical product is unique.

Design decisions in clinical development programs and trials rely on consolidating, analyzing, weighing, and prioritizing a broad range of sources of information from guidance, past experience, expert advice, and real-world evidence. This information is typically captured in an unstructured format, in the form of clinical development plans, protocols, documents, and presentations.

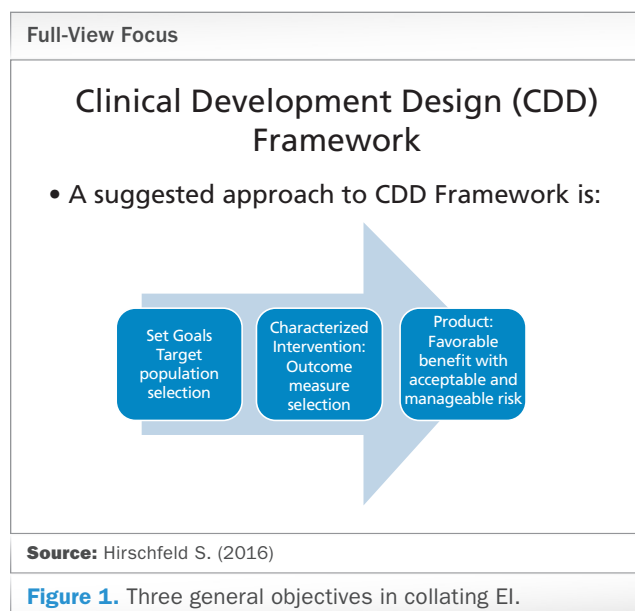
Such a process is not optimal. Designing a successful clinical research program can benefit from a robust and comprehensible framework, collaboration across many domains, generation, capture, and effective sharing of data and historical information, and relevant tools

The CDD Framework we propose encompasses the support for design-based decisions and how to apply them to a clinical development program. It should accurately tell the story of how plans, data, and information evolve during the full life cycle of a therapeutic product from before clinical testing, then entry into first-in-human dosing, followed by the clinical trials, marketing authorization, as well as the experience from postmarketing surveillance and subsequent studies.

This proposed CDD Framework is different from a Clinical Development Plan (CDP), which we define as the tactical execution of a research plan.

Mapping the CDD Framework

The CDD Framework provides a methodology for the organization and preservation of information critical to medical product development decisions, information we refer to as “enabling information” (EI). EI includes process data, timelines, costs, and resource burden, among other quantitative and qualitative items. EI exists at every phase of the process, from concept to non-clinical and clinical testing, through regu-



latory approval, marketing, and post-marketing surveillance. The complete EI is ideally a comprehensive representation of an entire medical product development program. Thus, the CDD Framework collates the EI and captures the perspectives of all stakeholders, scientists, administrators, care providers, patients, regulatory agencies, financial stakeholders, collaborators, and sponsors in the product development process. One approach to collating EI and populating the framework is to focus on three well-recognized, general objectives of medical product development (see Figure 1 on page 11):¹⁴

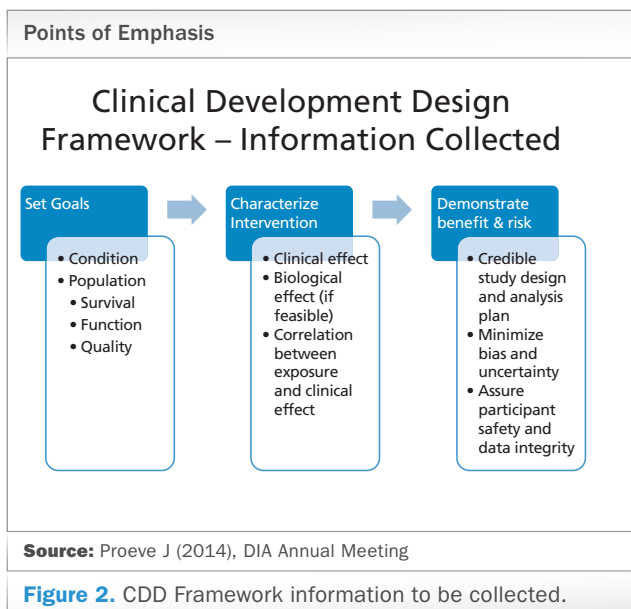
- Set goals that describe the product and patient population who will receive the product .
- Characterize the product administration (intervention) and define outcome measures (both efficacy and safety).
- Assess product viability against a benefit and risk profile.

These three well-recognized objectives of product development allow for a tentative mapping of our proposed CDD Framework. The following is a suggested approach to this mapping.

Goals and target population

When setting the goals, information on the condition (indication), the target population, and the expected benefit to that population is needed (see Figure 2).¹⁵ This step also requires a description of the product under development, as well as measurable endpoints that are connected to the objectives and measures. The target population is typically defined by phenotype and demographics, but one can also consider genotype, geographic location, age, or developmental stage and lifestyle.

Information generation and collection in this step may originate from many sources, including scientific and medical subject matter expertise, epidemiology, outcomes research, biostatistics, real-world data, and clinical operations.



Intervention and outcome measures

Characterizing the intervention requires investigation of its expected clinical and biological effects, and establishing a correlation between exposure and effect. These tasks will also require input from scientific and medical subject matter experts and statisticians. If relevant, a central role should be taken by experts in biomarker selection and analysis. This step requires an understanding of the nature of the intervention, dosing, and administration. Route, frequency, duration, and other parameters related to exposure need to be understood and documented. There needs to be a focus on defining informative and relevant outcome measures that vary with deterioration or amelioration of the clinical condition in a predictable manner. The clinical trial assessments must be feasible, acceptable, linked by time, and connected to the outcome measures.

Risk and benefit evaluation

There needs to be an emphasis on risk management, with assessments and outcome measures demonstrating an acceptable risk/benefit profile. This profile must be based on clinical trials with credible study design maximizing participant safety while minimizing bias and uncertainty as well as analysis of data assured of integrity.

Validation of design output

To determine that all aspects are covered in the design, the perspectives of patients, investigators conducting the trial, oversight bodies, regulators, and the sponsor should be reviewed. Table 1 (see facing page) gives examples of some of the aspects to be validated as the output of the design of a clinical trial protocol within the CDD Framework.

To summarize, the vast number of questions and ensuing answers required for each objective are interdependent and temporally linked. With that in mind, the design of the CDD Framework requires a comprehensive understanding of the design decisions and why these decisions were made. Each objective is supported by enabling data, consisting of regulatory information, early research and development data, clinical study data, epidemiological data, payer-focused data, and justifications.

The clinical design effort will not necessarily be a process in which goals are set, interventions characterized, and risk-benefit demonstrated in a linear fashion. As new information is generated that more clearly demonstrates aspects of the benefit-risk profile, the intervention, the condition, or the target population may become better characterized, leading to the setting of new goals. Also, at any given stage of medical product development or the life cycle management of a medical product, there will be key questions that remain unanswered, or the uncertainty about the outcomes based on the collected evidence may become greater than desired.

The CDD Framework captures these gaps and uncertainties, and helps moving forward by prompting the establishment of a logical plan for setting goals that will fill those gaps and decrease uncertainties.

The CDD Framework is intended to evolve into a knowledge base for the design of products supporting key design objectives, and to

facilitate the validation of those objectives. It should properly represent the interdependencies between design constraints, decisions, and information—and facilitate the communication of those relationships between stakeholders to ensure that the work designated in the CDD actually takes place.

Risk management

There are many types of risks to be addressed throughout the CDD Framework, each of which requires appropriate management. Besides risks relating to regulatory issues, risk considerations within CDD include those for business and scientific validity, as well as concerns such as loss of time, opportunity, effort, and reputation.

Certain risks will not be addressed in the CDD Framework, because those risks could not reasonably be attributable to aspects of design, such as reporting delays, data issues, misconduct identified, incorrectly enrolled patients at a site, etc. Moreover, the European Medical Association (EMA) notes that “risk management is a systematic process for the assessment, control, communication, and review of risks associated with the planning and conduct of clinical trials and clinical development programs.”¹⁵ The CDD Framework should help to identify risks to determine what can happen, when, where, how, and why—and to enable analysis of the likelihood of the occurrence and detection. Finally, there should be decisions on acceptable tolerance levels.

Tools: Design examples

Implementation of the CDD Framework can leverage many of the tools, methods, and technologies that have been applied to other areas of knowledge acquisition, storage, and analysis. Utilization of various combinations of these tools can enhance the power and interoperability of the CDD Framework for the capture of enabling information, decision options and rationale, and relationships of choices to outcomes.

Semantic technology

The conventional approach to store and access information is by categorizing and indexing information into relational databases based on static structures. XML-based data standards, such as those currently used in CDISC data capture and transfer standards, are designed for such structured data. A primary challenge here is that information associated with design thinking can initially be apparently unstructured, incomplete, or subject to further changes and definitions. However, similar to data standards, updates are inevitable.

Semantic technologies represent a family of technologies related to the capture, storage, indexing, querying, and classification of unstructured data governed by the World Wide Web Consortium (W3C).¹⁶ In particular, semantic technology allows the development of flexible information models, where concepts can have different meanings, links can be created between disparate information sources, and information is incomplete.

For semantic technology, well-defined rules are established that convey meaning to specific words.¹⁷ In doing so, an assortment of words that have the same meaning (as defined by semantic rules) allows for an overarching search with far greater returns than relying on

Key Validation Measures		
TRIAL INITIATION	CONDUCTING TRIAL	SPONSOR
Will the targeted population join the trial?	Are the objectives and outcome measures feasible and quality controlled?	Are the outcome measures supporting design and decision-making questions?
Are all measures collected useful for an informative analysis of the measures used?	Is the infrastructure adequate to support precise exposure delivery and collect, transmit, and archive high fidelity data?	Will the analyses be performed with sufficient timeliness and robustness to support decisions?
Are the data collected with sufficient fidelity, stringency, and completeness able to support the selected outcome measures?		

Source: Banach et al.

Table 1. Perspectives in validating the design prior to protocol developments.

a search for each individual word. Moreover, with linked web data, the user can search for information on the internet and circumvent the need to rely entirely on conventional relational databases. However, some of the linked data sources can be unstable, outdated/not maintained, difficult to discover and explore, largely undocumented, and/or time-consuming to establish.

The flexibility offered by semantic technology makes it well suited to be leveraged for the CDD information model. We need to obtain relevant information for input into the program design, as well as the intended protocols, appropriate data analyses, clinical study reports, and regulatory submission. These components, attainable through semantic technology, are incorporated in the CDD Framework in a comprehensive yet temporal arrangement.

Ontology

For any information model, a common vocabulary or ontology is a prerequisite. Ontologies help us to organize terms and define relationships, to enable reuse of domain knowledge and separate domain knowledge from the operational knowledge.¹⁸ Ontologies organize domain knowledge in a common structure of entities and their relationships.¹⁹

An example of applying ontologies for semantic data supporting clinical research is the ontology for FDA regulations in the Resource Description Framework (RDF), being created by the PhUSE Reg2RDF group.²⁰ Currently, the work focuses on indexing 21 CFR terms and evaluating the key phrases and presenting a web interface. The best way to organize the review process is part of their development process. The CDD Framework aims to apply a similar approach for establishing a corresponding ontology.

In order to develop the CDD ontology and to begin mapping the design process, we can start with the checklists from the FDA (including the TPP and prescribing information labeling templates and checklists)

and quality by design reference tools from the Clinical Trials Transformation Initiative (CTTI) as well as other data sources.^{21,22,23}

Before we can apply the terms, we must follow the examples found in developing biomedically-based common data elements (CDE).¹³ We need to bring together all of the above terms in a single resource with links, redundancies, and hierarchical relationships. Our starting place in building our ontology is Vanderbilt University’s Research Electronic Data Capture (REDCap) application.²⁴ This application allows us to capture redundancies and provide links between the terms that we are referencing.

Cmap — concept mapping tools

A semantic information model can serve as the backbone for software applications. However, a visual representation of the CDD Framework can also serve as a guide for design teams on its own. A two-dimensional open source concept mapping tool is available from the Florida Institute for Human & Machine Cognition (IHMC).²⁵ Using this software, we will be able “construct, navigate, share, and criticize” our models of the CDD Framework. Cmap tools allow us to not only share our concepts and understanding of the CDD Framework, but to link our maps to related concept maps and other types of media.^{26,27}

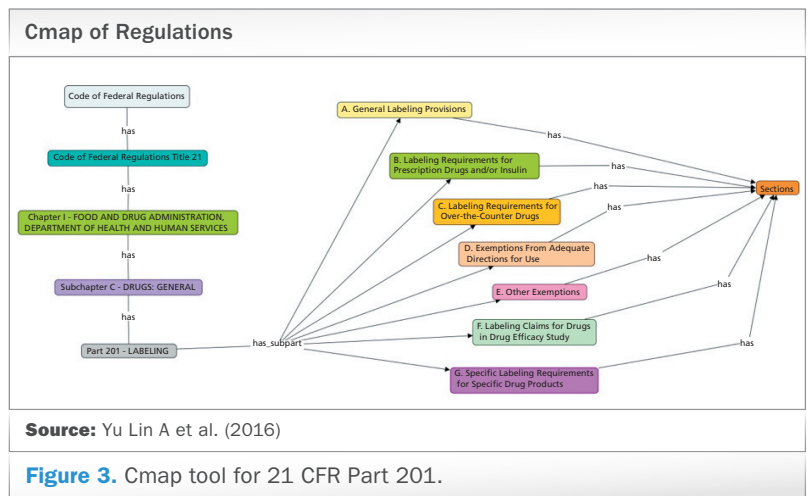
Figure 3 maps the FDA’s 21 CFR Part 201 regulations with the Cmap tool.²⁸ We can then hyperlink and download each of these sections of the regulations. For the CDD Framework, we can develop Cmaps for each of our areas: setting goals, characterizing the intervention and delivering the medical product, and link the information that medical/scientific, operations, and regulatory groups need for their work.

Visual interactive information model

The Cmap concept maps give us a two-dimensional mapping. The next step beyond the two-dimensional concept maps is the work done by Kerstin Forsberg and Maria Benjegard with Neo4j mapping.²⁸ This tool allows for multi-dimensional modeling and linking.

Figure 4 (see facing page) depicts the concept of a visual, interactive information model representing the interdependencies between activities, information, and decisions.

The medical product development data and metadata entails collection of the required factors describing not only what, where, and when a decision was made by one or all of the stakeholders, but also what alternative decisions were proposed, why these were proposed, and why these decisions were accepted or rejected. In order to support the development of reproducible design-based decisions, the data and metadata for supporting decisions must be detailed and accessible. The value of the CDD Framework is dependent on easy application of this information model. We envision that it will facilitate robust design decision support, including toolsets. However, an interactive visual model can also directly contribute to the understanding and representation of the process.



Systematic collation of EI depends on application of CDE, collection and defining of easily retrievable data, and conforming to definitions that are agreed to by design stakeholders.¹³ Through the identification of enabling information, the components of clinical design may be assembled into a framework that optimizes a particular use case and establishes the possible reuse of and learning from the decision-making process.

To maximize the utility of enabling information, it should be collected with fidelity, quality, stringency, and timeliness.

Regulatory Interactions

A clinical development program framework exists within an environment under the oversight of regulatory agencies. A general hierarchy regarding authority and legal enforceability is as follows:

- Statutes are binding and generally describe principles and goals to achieve an outcome such as assurance that products intended for human medicinal use are safe and effective. In the US, they are developed by the legislative branch and signed by the executive branch. They are binding and legally enforceable.
- Regulations are based on statutes and generally provide further details on implementing the intent of the statutes. Regulations are developed by the executive branch. They are binding and legally enforceable.
- Guidance documents are developed by individual agencies and represent a default recommendation for applying laws and regulations to particular topics. Guidance documents are usually not binding; however, variance from agency recommendations usually is expected to be supported by a scientific, logistical, or other rationale.
- Specific agreements between a party and an agency, such as a special protocol assessment, are on a case-by-case basis and considered binding.

In the CDD Framework, the interactions between data, scientific principles, regulatory principles, business decisions, and value decisions can be captured, analyzed, displayed, and used to inform future decision-making.

A regulatory agency as a partner for input and agreement on any product development plan is an important expectation. The CDD Framework for a particular medical product or planned indication can offer valuable insight and allow knowledge-sharing about the product.

The overall design of a product development program from inception to postmarketing success is important for regulatory review, because every development program activity needs to be compliant with the regulatory environment(s) and expectations in which the medical product is intended to be studied and marketed. The CDD Framework can provide a blueprint for a regulatory review team to evaluate a proposed program and may suggest metrics for comparison with programs for the same class of medical products for the same condition or for similar populations. These will help identify potential remedies to address deficiencies.

Integrating a target product profile and the CDD

A target product profile (TPP) is a format for a summary of a drug development program described in terms of labeling concepts that may be very helpful in its program design.²¹ While its submission to a regulatory agency is voluntary, a pharmaceutical sponsor may share a TPP with the agency to facilitate communication regarding the design for clinical development.

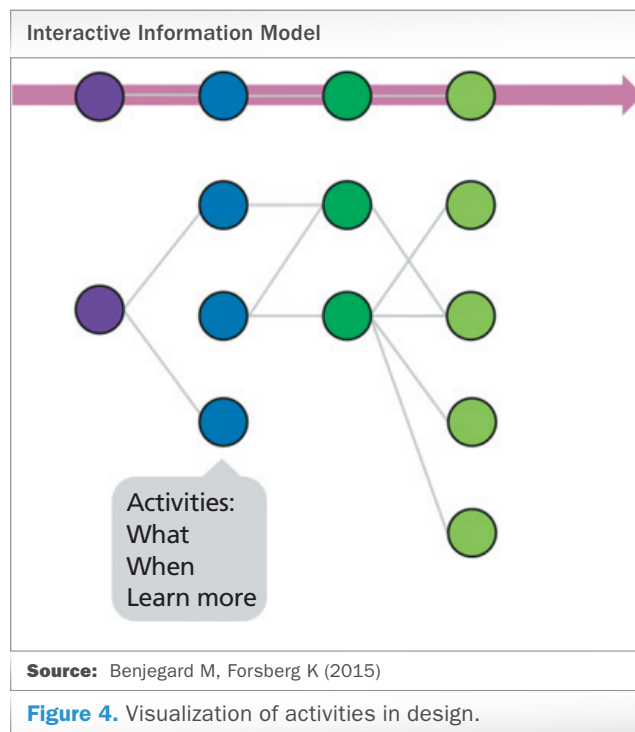
The FDA has provided a guidance document detailing the labeling concepts in TPP and suggestions for what should be addressed in the label.²¹ Sponsors often want more information on adequately addressing these concepts during clinical development. More information can be found in checklists from the FDA, such as the “Selected Requirements of Prescribing Information” (SRPI) checklist, which details 41 required and optional items for the labeling of drugs and biologics.²² When fully developed, our CDD Framework may offer us a link between the TPP and these checklists. Other potential advantages could be the linking of the TPP with quality by design and risk assessment tools.^{23,29}

When using the TPP, the CDD Framework needs to include details about these labeling concepts: indications and usage, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, adverse reactions, drug interactions, use in specific populations, drug abuse and dependence, overdosage, description, clinical pharmacology, nonclinical toxicology, clinical studies, references, how supplied/storage and handling, and patient counseling information. Recommendations to address these concepts can be found in the FDA guidance document on the TPP.²¹

As discussed above, one may be able to link recommendation in the TPP guidance to the SRPI checklist to ensure compliance with the labeling regulations.

Discussion

With the increasing challenges associated with successfully completing drug development, which includes issues about attending to medical product launch and postmarketing surveillance, contract research organizations (CROs) and pharmaceutical companies have started to explore ways to improve clinical development design decision-making. Automation has aided the execution, management, and reporting of clinical trials, but this can only contribute partially to efficiency. The



clinical research community has realized that expert scientific and regulatory guidance, information enabling decision-making, and retention of project memory are necessary for successfully completing drug development.

A design paradigm can be summed up by four key steps: “Define – Integrate – Prototype – Crystallize.”³⁰ Prototyping and crystallizing would require the integration of accessible evidence, which may include real-world evidence. The process starts with defining and framing the problem questions in order to identify clear and appropriate objectives. Access to historical actual evidence and data are needed. Tools are also needed to enable calculations, visualization of design concepts, and engagement of all the stakeholders through clearly defined and stated goals.

Technologies that easily link design components and decisions to the information/data are needed in clinical development to overcome the unavoidable loss of historical knowledge. Even with existing technologies that allow for the creation of relationships between design components and the capture of “decision points,” one can only capture the final decision, the rationale, and/or supporting data in text-based minutes of meetings.

There is often the intent to transcribe the information from documents such as meeting minutes to a better system, but competing needs generally prevail regarding resource allocation. Thus, the technology must be easy to use and not time-consuming. It must be intuitive so that teams can capture the relevant information in real-time during the design meetings. The teams must be tasked with not only capturing information around decisions implemented in the design, but also what was not implemented, thus preserving design alternatives for future consideration.

The following are issues relating to the CDD Framework which organizations need to consider:

- What are the key decisions to be made during a product development life cycle?
- How is the enabling information captured, archived, and analyzed?
- How is the enabling information made available for review of the ongoing project and for future projects?
- How can information be captured in real-time?
- Is there something we can decide that does not need documentation? If so, how is that decision reached?
- How do we document the decision not taken?
- Reproducible design decisions—given the same information, will we always come to the same conclusion? What other factors influence decision-making?

We embark on an endeavor that, as noted by Kahneman, is spreading across all industries to reduce “noise” and improve decision-making.⁸ Our goal is to develop a framework and a knowledge base of linked data on the CDD Framework that will serve as an information model for clinical research stakeholders, including considerations for regulatory input and risk assessment/management. This is a first step in providing collaborative tools for CDD-based decision-making and establishing the validity and applicability of the model.

We are currently working on adapting tools, including a CDD ontology, to be used to map and implement the design and decision-making process.

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The Impetus for Natural History Studies in Rare Disease R&D

Thomas Ogorka, Gajendra Chanchu

The use of natural history (NH) studies early in clinical research can help facilitate development programs for orphan drugs.

More than 7,000 rare diseases have already been identified, and this number is rising. The number of patients diagnosed with a rare disease will gradually increase as we move toward better and advanced diagnostic methods and genetic testing being able to identify people with rare disorders.

One of the two main reasons that prompt the development of new drugs for rare diseases include the human need, i.e., an unmet medical need for millions of patients suffering from a rare disorder. The healthcare industry must invent new drugs to improve the lives of patients suffering from rare diseases. The second important reason is the sales opportunity for the developer once such drugs are introduced to the market. Worldwide orphan drug sales are forecasted to total \$209 billion by 2022, which will represent 21.4% of worldwide prescription sales, excluding generics (see Figure 1 on facing page).

The market for cystic fibrosis, for example, will grow rapidly at a compound annual growth rate (CAGR) of 30.6% over the period of 2012-2019.¹

To obtain marketing approval, regulatory agencies across the globe require data from appropriately designed and controlled clinical trials for a new drug. Conducting clinical studies in rare diseases, however, is challenging for several reasons, some of which include unavailability of adequate number of patients, few experts in rare diseases, lack of validated biomarkers, poor understanding about the disease, lack of methods for diagnosis, and unavailability of historical information. To strengthen the understanding of rare diseases and their natural course of disease progression, it is essential to conduct natural history (NH) studies to support the clinical development program for orphan products.

What are NH studies?

The NH of a disease is the natural course of a condition from the time immediately prior to its inception, progressing through its pre-symptomatic phase and different clinical stages to the point where the disease has ended without external intervention. NH studies track the course of a disease over time, identifying demographic, genetic, environmental, and other variables that correlate with its development and outcomes in the absence of treatment. Thorough understanding of a disease's NH is the foundation upon which a clinical development program for drugs, biologics, medical foods, or medical devices is built.²

Why are NH studies required?

Due to the lack of sufficient historical data to understand the clinical characteristics and NH of the disease, rare diseases are often poorly understood and there is a lack of availability of suitable data which can be used to design clinical development programs for a potential drug to treat the condition. As rare disease trials require more careful and rigorous planning, one of the initial plans should be to collect NH data that can be crucial for the entire drug development program.

Often considered the same as registries, NH studies are different in their definition and application in the overall drug development program. Registries are broader arrangements to collect data in the form of setting up the database and collecting general information about the patients, e.g., contact information, or they may be conducted as a post-marketing commitment to collect safety and efficacy data.

However, NH studies are comprehensive, granular, and more specific toward collecting useful data on disease



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characteristics, its manifestation, and its natural course of progression to guide future research.

The main purpose of NH studies is to collect useful information to facilitate and advance drug development programs; however, in exceptional circumstances, NH study data can be used as a historical control. This may happen in special circumstances when the disease has a higher mortality and the intended drug has an immediate strong effect in reducing the mortality or in improving the patients' lives. Even in these cases, the regulatory agency may not permit NH data to be used as historical control and such requests need to be discussed with the agency on a case-by-case basis.

When should the NH study be conducted?

Drug development for any disease is a time-consuming and costly process; however drug development for rare diseases is predominantly complicated due to challenges associated with it and the usually high per-patient costs. Conducting an NH study at an early stage of the clinical development program helps sponsors to define the study strategy by developing a valid and robust protocol. The comprehensive understanding of the disease can save a significant amount of time, money, and resources. Starting the clinical development program without having useful data from the NH study is one of the most significant reasons why rare disease trials fail. The FDA advises sponsors to evaluate the depth and quality of existing NH knowledge early to make well-informed decisions in the drug development process.³

Types of NH studies

NH studies can be retrospective, prospective, or both. Typically, NH studies are a combination of retrospective and prospective data collection.

Retrospective chart review is useful and often necessary to collect the required data to understand the NH. However, retrospectively collected data have some limitations. They may be less accurate and inconsistent and, therefore, appear to be less reliable, e.g., useful information pertaining to disease history or concomitant medication might not be reported in the medical charts and there may be no other source to collect that information. The other administrative challenge would be to get access to the medical records. In some countries, medical records are available in electronic format and can be accessed through the institute and/or treating physician; whereas in most other countries, medical records are still in paper format and may not be with the patient or in one location. Patients, in these cases, may have been seen by multiple specialists across different institutions and, as a result, collecting this scattered information can be very challenging and time-consuming.

Conducting an NH study at an early stage of the clinical development program helps sponsors to define the study strategy by developing a valid and robust protocol.

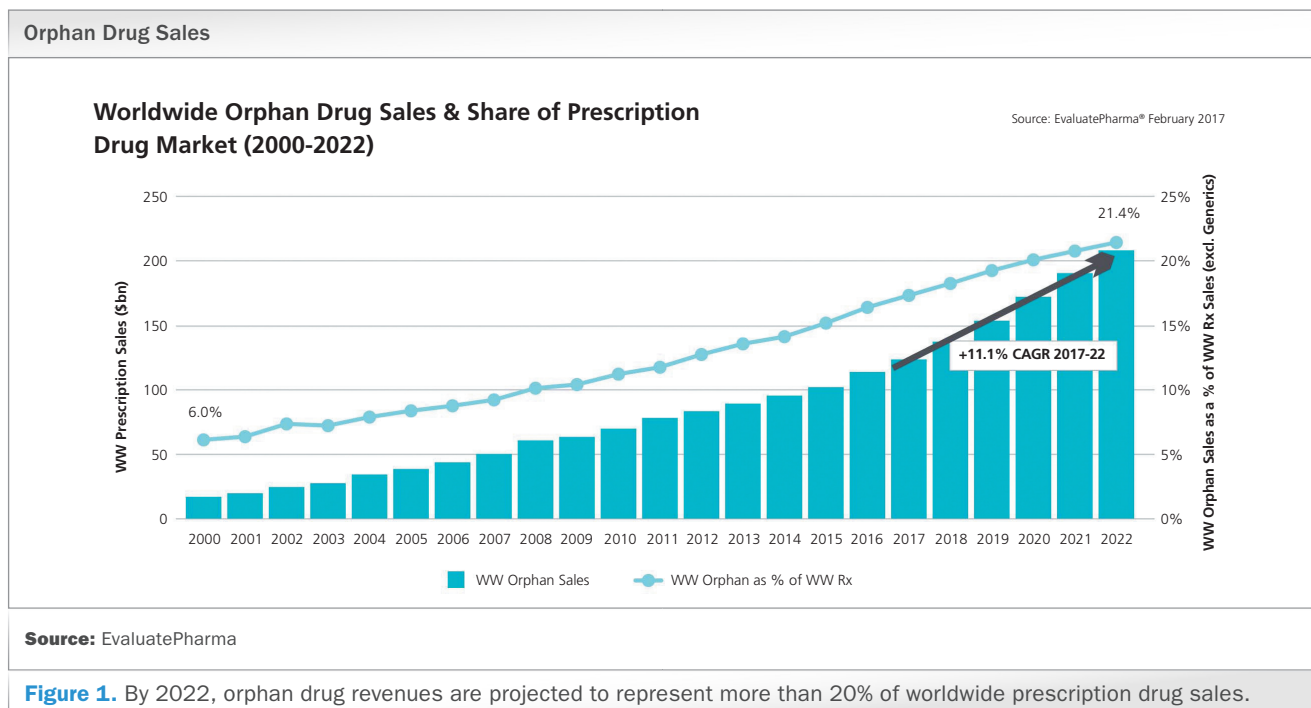


Figure 1. By 2022, orphan drug revenues are projected to represent more than 20% of worldwide prescription drug sales.

For ultra-rare diseases, the patient collective will be even smaller and sponsors may also need to collect retrospective data of deceased patients.

A prospective longitudinal NH study collects data in follow-ups and is more useful in collecting the NH of the disease. Such studies may run for decades to continuously collect data of disease characteristics.

An example of a longitudinal study is The International Collaborative Gaucher Group (ICGG) Gaucher Registry, which aims to enhance the understanding of the variability, progression, and NH of Gaucher disease, with the ultimate goals of better guiding and assessing therapeutic intervention, and providing recommendations on patient care to the medical community that will improve the outcomes for patients affected by this disease around the world. It started in 1991 and to date has enrolled more than 6,500 patients at more than 700 sites. Analyses of the extensive body of longitudinal data have increased the knowledge of the disease in a broad range of topics, including the NH of Gaucher disease; phenotypic and genotypic variation among patients; diagnosis, treatment, and management of the condition; disease manifestations in children; long-term treatment outcomes for ERT; bone disease and complications associated with the disease; and neuroopathic Gaucher disease. Data generated from the registry have been published in nearly 30 key articles and have provided much-needed and important insight into this rare genetic disease.⁴

At times, sponsors may collect data to explore disease characteristics by taking a snapshot of data as it stands at the time of study. Such studies are called prospective cross-sectional studies.

Patients play a vital role in an NH study, as the entire foundation of these studies is built on the idea of data collection from patients suffering from a rare disease.

Cross-sectional studies provide a moderately detailed understanding of the disease and can be valuable for developing outcome tools; however, they do not provide any details about the pace of the disease progression, whereas prospective longitudinal studies provide the most comprehensive understanding of a disease, its course, and pace of progression. Cross-sectional studies are easier to conduct than prospective longitudinal studies, as the latter requires long-term commitments from patients, investigators, and other stakeholders and, hence, may extend the overall drug development timelines.⁵

How should an NH study be conducted?

Initiating and planning

- At the planning stage of an NH study, it is important to reach out to all stakeholders (i.e., investigators, industry representatives,

patients/caregivers, patient advocacy groups, etc.) to seek their opinion/feedback, ensuring there are well-defined objectives and then to delineate the strategy and tactics as well as the action plan to meet the study objectives.

- Initially, the stakeholders may assess the limited knowledge about the disease characteristics and what is expected to be achieved from the NH study. The study should start with the broader criteria and as the study progresses, more specific objectives can be set. Thus, the initial plan needs to be progressively elaborated as more information becomes available.
- Other aspects of the NH study that need to be considered are the data collection method, the frequency and type of data to be collected, and other areas with regards to scope, time, cost, quality, and risk management.
- Communication with regulatory agencies is important. The developers must share their objectives of conducting the NH study with the agencies and seek their opinion and direction.
- The FDA Critical Path Innovation Meeting (CPIM) is a means by which the Center for Drug Evaluation and Research (CDER) and investigators from industry, academia, patient advocacy groups, and government can communicate to improve efficiency and success in drug development. The CPIM can assist in the design of NH studies to increase the potential for the data generated by these studies to help in the design of interventional clinical trials and drug development programs.⁶
- The European Medicines Agency (EMA) also has launched initiatives to encourage small and medium-sized enterprises to seek scientific advice at an early stage of drug development to increase the chances of obtaining marketing authorization.⁷

Operationalization

- A successful NH study requires commitment and rigorous efforts from all involved stakeholders to be able to provide meaningful data.
- There are various methods for setting up and running NH studies. Some studies may require patients/caregivers to complete questionnaires, which can either be completed online or sent to patients/caregivers with the request to return the completed ones. The advantage with such an “off-site” process is that patients/caregivers are not required to visit the sites, whereas other studies may include protocol elements that require patients to undergo certain procedures at the site (e.g., diagnostic tests, activity assessment, etc.). It is important to take into consideration the burden of invasive tests on the patient, with the aim to limit these. Patient advocacy groups can provide valuable information as to what, in a practical context, will be acceptable and doable.
- As the number of expert doctors in the field of rare diseases is limited and since they are mostly located at larger treating hospitals in bigger cities, patients must usually travel further to these identified centers. Such a setup requires continuous engagement from the patients and, therefore, those that implement the study should consider an action plan for keeping patients engaged and encouraged. This includes travel reimbursement for the trial participants and arrangement for their travel, i.e., airlifting the patients/caregivers/families.

- Patients play a vital role in an NH study, as the entire foundation of these studies is built on the idea of data collection from patients suffering from a rare disease. The community of rare disease patients and caregivers like to connect with other patients and families affected by the same disease, while participating in the NH study. It is known to patients and families that there is no therapeutic advantage from their participation in the NH study; however, their participation will help to advance future drug development efforts. Patient advocacy groups support patients/families by providing them with information, resources, and services, and encourage their continuous engagement in the NH study.
- Patients and families participating should be encouraged for their participation and, hence, patient groups play an important role in identifying patients and keeping them interested in these studies.
- The sponsor should initially have a broader perception to assess more biomarkers and outcome measures. Due to diverse clinical characteristics, one patient may demonstrate a set of symptoms that are very different from the other patient suffering from the same rare disease. As more data are collected, the developers can decide upon the appropriate biomarkers and outcome measures for the clinical development program.
- NH studies are intended to be disease-specific and not therapy-specific. It is imperative to understand that sponsors may face challenges in rigorously following regulatory requirements such as good clinical practice (GCP) for such studies. This does not lessen the importance of quality data from these studies, as the most important objective of any NH study is to enable the sponsor to make informed decisions about the drug development program. Data of poor quality may be misleading, which can harmfully impact the overall therapy development program. This makes it important for the sponsor to consider monitoring of data on an ongoing basis, although the required frequency and extent of monitoring may differ from one study to the other.
- Conducting NH studies in rare diseases can be costlier than anticipated and may result in sponsors not being able to fund such studies. As there is an immense importance of conducting such studies to support the overall drug development process, government programs have been put in place that encourage and assist with the design, funding, and implementation of NH studies.

The goal of FDA's Orphan Products Natural History Grants Program, for example, is to support studies that advance rare disease medi-

cal product development through characterization of the NH of rare diseases/conditions, identification of genotypic and phenotypic subpopulations, and development and/or validation of clinical outcome measures, biomarkers, and/or companion diagnostics.⁸

Conclusion

NH studies, which provide comprehensive information about a disease, are an essential element for orphan drug development programs. Conducting NH studies requires careful planning, and significant thought needs to be invested to make them achievable. Rare disease drug development is challenging and requires a lot of patience, money, resources, and time; however, it can be rewarding for all parties involved. Conducting NH studies is the initial and important step aimed at supporting the orphan drug development process. It gives a ray of hope to patients affected by a rare disease and their families and informs them that the process of finding a therapy has started.

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MythBusting: 6 eConsent Myths We Need to Correct in 2018



While many myths often go unexposed, the industry is working to rectify the facts about electronic informed consent.

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The average human swallows six spiders over the course of their lifetime. Gum takes an average of seven years to digest, and electronic informed patient consent isn't permitted in a variety of countries. What do all three of these things have in common? They're all myths. The first two are harmless and are easily debunked by a quick Google search. The third however, has the potential to negatively impact a patient, a site, or a clinical trial. Here's a quick list debunking six of the most common myths we've heard regarding electronic informed consent.

1. Myth: Electronic informed consent isn't widely adopted. A 2014 WIRB Copernicus Group study showed that over 66% of the top-50 pharma companies had tried electronic informed consent back in 2014, with 100% of the top 10 piloting it as well. Some large pharma have chosen to switch entirely to electronic patient consent for all future trials.

2. Myth: Many countries don't support it. This is false. It's important to note there is no regulation from any country currently that prohibits the use of electronic informed consent.

There is regulation in select countries that prohibits the use of electronic signatures. Fortunately, these regulations don't affect the use of electronic informed consent, because paper signatures can be easily scanned and uploaded into a clinical operations system for documentation and audit purposes. This approach can allow use of electronic informed consent worldwide without issue.

3. Myth: Sites dislike it. Based on our own site survey data, sites disliking electronic informed consent couldn't be further from the truth.

In fact, sites love electronic informed consent because it helps sites and patients focus on concepts or issues with which they're having trouble, which improves the quality of conversations and questions during the consent process. Sites have also reported they appreciate the reduction of paperwork, the ability to provide patients with a multimedia eICF for viewing at home, and the convenience/quality of life dashboards and reports provide.

4. Myth: It's too difficult for seniors. In a 2016 study conducted by Janssen, seniors "universally reported high satisfaction on each eConsent feature, finding the process 'easy' or 'very easy.'"

In a 2013 National Center for Biotechnology study, 80% of 160 women age 65 or older were "able to complete all screening questions consistently and showed a nonsignificant trend toward greater ease of use and willingness to spend more time in their physician's office compared to those using IVRS." The study concluded the women "found good satisfaction and feasibility with a tablet computer interface for the recruitment and screening of patients for a hypothetical osteoporosis PCT in community office settings."

5. Myth: It's too expensive for most studies.

While there are certainly costs associated with a full-service electronic informed consent model, these costs are mostly over reported. In many instances, sponsors reporting high costs for electronic informed consent are reporting the combined costs of using paper and electronic informed consent at the same time, and as separate processes. For most studies, the costs of electronic informed consent are comparable to managing the costs of a paper consent process.

6. Myth: Electronic informed consent takes a lot longer than paper. Those who say that the paper process is quicker may not be accounting for the total amount of time saved across the entire informed consent process.

Both sites and sponsors have reported an increased time savings when using electronic informed consent due to its ability to author ICFs, manage approval chains for documents, employ workflow management controls, directly integrate with IxRS, CTMS, and eTMF systems, and automate the audit process through system-wide tracking and creation of all audit documents.