COMMENTARY

Tangential headwinds when integrating industry-funded clinical trials into a US health care delivery system

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Abstract

Although there are regulatory obligations put forth by the US Food and Drug Administration (FDA) that directly govern clinical trials and other investigational therapies, such activity does not occur in a vacuum. There are other regulations and administrative policies that are tangential to the operations of clinical trials in a health system that can have a direct or indirect effect. Regulations such as HHS’s Common Rule and Right To Try have been rapidly evolving over the past couple of years. Also rapidly evolving in this timeframe are the federal government’s administrative branch policies involving incentives and disincentives for electronic health records as well as how quality is measured electronically. All of this is occurring as the entire health care delivery sector is trying to reinvent itself with both existing and new unexpected players. Thus, while those interested in conducting industry-funded clinical trials in their health system generally know to keep up with FDA, they must also be diligent to see how the greater system is forced to evolve to assure that they remain successful form a regulatory and operational standpoint.

KEYWORDS
clinical trials, health care, regulation

1 | INTRODUCTION

Being asked for the first time to be a site in an industry-funded clinical trial can be an exciting event in a health professional’s career. Shortly after the alluring invitation, however, hits the reality of integrating it into the busy health care delivery setting that was never operationally, economically, or technically designed to support such an interruption from the business-as-usual. While the trial materials and newly discovered US Food and Drug Administration (FDA) regulations will require a lot of learning in-and-of-themselves, the health care setting of which it will operate in (be it a hospital, clinic, or otherwise) is challenged to reevaluate its homeostasis to accommodate the individual nuances required for the successful conduct of the protocol. This does not come without regulatory, technical, and economic/operational headwinds that come as a surprise to those who focus exclusively on FDA regulations. Herein, we will review some current friction or other interesting anomalies faced by health care delivery systems in the United States that either add to the challenges of conducting an industry-funded clinical trial or provide outright disincentives. These specific areas were selected as they are among the most impactful and rapidly evolving ones.

2 | THE REVISED COMMON RULE

The Common Rule (which is named as such because it is the research governance rule shared across 16 different federal agencies, including the Department of Health and Human Services, which codifies the regulation at 45CFR46) regulates federally funded research with human
subjects. Although the FDA is an agency that organizationally falls under a Common Rule adopting agency (Department of Health and Human Services), the FDA has existed with similar but independent regulations concerning Informed Consent and Institutional Review Board oversight (respectively 21CFR50 and 21CFR56). With that said, it is important to note that for many reasons, it is not uncommon for governmental, public, and private institutions to adopt Common Rule provisions voluntarily for nonfederally funded studies which, in effect, imposes an overlap of Common Rule provisions onto FDA-governed studies. Therefore, changes, guidance, and enforcement activities related to the Common Rule, although not directly affecting FDA-only-governed research, tend to eke into both the institution’s and IRB’s execution of FDA-governed activities. In addition, according to Section 3023 of the 21st Century Cures Act, the Office for Human Research Protections ("OHRP" is HHS agency that writes and enforces the Common Rule) and FDA must, to the extent practical and consistent with their statutory provisions, harmonize their human subject protection regulations within 3 years of the passing of the act (which passed in December 2016). It is currently uncertain as to how the agencies will reconcile the differences between the regulations that must be reconciled. However, there have been major initiatives by OHRP to initiate the changes.

In July 2011, OHRP published an Advance Notice of Proposed Rulemaking proposing the biggest changes to 45CFR46 (a.k.a. the "Common Rule") since the issuance of the Common Rule itself in 1981. After comments were fielded, this evolved into a Notice of Proposed Rulemaking in September 2015 with the final rule being posted January 2017 to come into effect on January 19, 2018. On January 17, 2018, it was published that there was to be a 6-month delay in the effective date (postponing it to July 19, 2018), and on June 18, it was delayed again until January 21, 2019 (although allowing for some minor options to be adopted in the interim). Many aspects of the revised Common Rule are either completely askew of or minimally impactful to FDA-governed studies. However, certain revisions as described below are of key interest, as they undoubtedly will eke into FDA-governed studies at the institution and IRB level.

The revised Common Rule adds four new required elements of consent as specified in Table 1. The first (45CFR46.116(b)(9)) applies to all research, and the remaining three are to be added when applicable. As can be clearly seen, each of these generally are attributable to nearly all FDA-governed research and thus would affect its conduct (and post-conduct) when adopted to FDA-governed, industry-funded clinical trials.

As industry-funded clinical trials are often conducted with the intent to publish and/or submit the data to regulatory authorities across the globe, the demands for data transparency make it nearly impossible to commit to not de-identifying the dataset for future use. For example, European Medicines Agency Policy 0070 requires the manufacturer to make anonymized individual level data available, and Health Canada has posted a draft regulation to do the same. Additionally, while some medical journals have required data sharing plans of varying degrees as a condition of publication, effective July 2018 all (approximately 4000) medical journals falling under the International Committee of Medical Journal Editors (ICMJE) will be required to submit a data sharing plan in order to have the clinical trial results considered for publication. Secondary or subsequent use of the data may be prohibited (1) intentionally by the research subject or (2) perhaps even unintentionally by the researchers themselves if the informed consent document from the original research project either does not address secondary use or even has statements implying there will be no such use (and resultantly inhibit a publication or regulatory filing).

It will also be interesting to see how the remaining new statements will affect recruitment into clinical trials should they be adopted. For example, a statement requiring the addressing of any profit sharing plans when biospecimens are used introduces a new dynamic between the patient, provider, and manufacturer rarely addressed before in the consent process. Hypothetically (under the assumption that the status quo of profits not being shared will remain), calling this to the forefront may agitate any distaste for the commercial realities of medicine and negatively affect recruitment. The remaining requirements similarly add new dynamics and introduce extra-study operational requirements and/or limitations on both the site and manufacturer should they be adopted.

The revised Common Rule also formalizes in regulation an option of what many called “Front Door Consent” but OHRP calls “Broad Consent.” At the risk of oversimplifying the concept, this type of consent is generally intended to have a person opt-in to having their data used for unknown/unspecified secondary research purposes as opposed to today’s standards where the information can be de-identified and used without the person’s consent for doing so each time, providing research, privacy, and de-identification regulations are met. Broad Consent in a health care provider’s environment occurs essentially when a patient has a health care encounter with that provider and they are requested to opt-in to having the health information generated used for secondary research. Much has been written about the complexities and complications of instituting the

| TABLE 1  | Four new required elements of consent under the revised common rule |
|-----------|---------------------------------------------------------------------|
| 45CFR46.116(b)(9): "One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens: (I) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or (II) A statement that the subject’s information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies." |
| 45CFR46.116(c)(7): "A statement that the subject’s biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit." |
| 45CFR46.116(c)(8): "A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions." |
| 45CFR46.116(c)(9): "For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen)." |
Broad Consent option, especially about, setting aside the nuances of the identifiability of the information, how an institution offering Broad Consent must be able to have the metadata infrastructure in place to allow the prevention from secondary use (even under an IRB Waiver of Consent/Authorization) of the related information and/or biospecimens pertaining to those who were offered such Broad Consent and refused. This mechanism of protection is growingly complicated in a world where data sharing is becoming more pervasive. In other words, it is not only challenging to conceptually strike the balance of each individual's desire for the use of their data with the necessity of the use of that data for the advancement of medicine. Even if such a challenge could be met, doing so in a manner that is not cost or operationally prohibitive seems even more the challenge. While much more could be written about Broad Consent outside of what impact it may have on FDA governed research, it is fair to leave it with the fact that institutions that choose to enact the Broad Consent option will likely have supply constraints on the secondary use of biospecimens and information for FDA-governed research and possibly additional limitations that the manufacturer must know about based on the content of the Broad Consent document.

3 | EXPANDED ACCESS AND “RIGHT TO TRY”

While providers can facilitate a patient’s access to investigational treatments through clinical trials, the FDA also grants access outside of clinical trials through their Expanded Access regulations. As does making a product available under a clinical trial, Expanded Access also requires some paperwork with the FDA as well as informed consent and IRB oversight similar to that of a clinical trial. Unlike a clinical trial, Expanded Access is usually requested for a single patient and the manufacturer usually places the burden of the FDA paperwork (eg, the Expanded Access IND request) onto the treating provider. With the growing number of requests for Expanded Access over the past few years, the FDA has in tandem made the requesting paperwork for physicians much more streamlined (in 2016, the FDA replaced the so-called 100 hour form that physicians had to complete with Form 3926, which is touted as a “45 minute form”) as well as publishing guidance in 2017 stating that the IRB chair alone can approve the access in lieu of waiting for a convened board meeting of the IRB.

In addition, there is recognition outside of the FDA for the need of Expanded Access. The Reagan Udall Foundation, a private organization closely affiliated with the FDA, has created their Expanded Access Navigator for both patients and providers to assist them in navigating the Expanded Access process. Additionally, Section 3032 of the 21st Century Cures Act requires pharmaceutical manufacturers to publicly post their policies for Expanded Access of their investigational drugs including how to make a request, their criteria for granting Expanded Access, and a hyperlink or other reference to information about the product requested. Despite the education efforts to increase patient and provider awareness of what is available under Expanded Access and how to obtain it, the overarching theme remains that it should not interfere with the clinical development of the investigational drugs. Nevertheless, if a patient wants the product, the provider wants to administer it, the manufacturer is willing to provide it and the FDA is willing to allow it, and the patient can receive it outside of having the institution set up as a site for a clinical trial.

Despite the FDA granting >99.5% of the requests for individual patient Expanded Access and demonstrating how they add value by providing dosing, adverse effect and other information that is not generally known to the provider, a subset of advocates believe that the FDA should not be involved in the equation. While historic attempts to remove FDA from the equation at the judicial level did not result in their favor (eg, those attempted by the Abigail Alliance in 2005-2008), newer advocate groups have changed strategy and campaigned to each individual states to pass a state “Right To Try law” under the guise that once the state passes the law, the FDA is no longer required. As of this writing, 40 states have passed their version of the law and despite the stated intent of trying to make it easier than going through the FDA to access the products, nearly each state adds their own extra individualized requirements above what the FDA requires, ironically making access under their Right To Try law more difficult than going through FDA's Expanded Access program. Much has been written about the appropriateness and effectiveness (or ineffectiveness) of this state law strategy, but nevertheless, it has increased public and provider awareness of the FDA’s Expanded Access program. For example, a patient unaware of FDA’s Expanded Access program hears on the news that their state passed a “Right To Try” law, demands a certain investigational product, receives the product, and walks away linking their success to the Right To Try law but not being interested in exactly what paperwork has to be done was oblivious to the fact that the manufacturer and provider went through the FDA’s Expanded Access process instead of trying to exclude the FDA via the state Right To Try law.

For a multitude of reasons, especially as any success is clearly limited with only state legislation that is in apparent violation of federal laws, the advocates have received the attention of the federal government who in May of 2018 passed legislation amending the Food, Drug and Cosmetics Act to allow the state “Right To Try” pathway to occur without FDA oversight. Regardless of whether this option is adopted by manufacturers, this effort (coupled with the growing information and communications about investigational products that the Internet and social media fuels that not existent a decade ago) providers are faced with a growing number of requests for pre-approval products outside of clinical trials, and it is, at least through FDA’s Expanded Access program, becoming easier to provide them.

4 | ELECTRONIC CLINICAL QUALITY MEASURES (eCQMS)

Over the past decade or so, the Center for Medicare and Medicaid Services (CMS) has evolved in their provider “report cards” they post on their website. The report card is not only used by the public to compare a provider’s scores against any other on the country, it is also used in certain “value-based purchasing” (a.k.a. “pay for performance”) meaning lower scores could translate to lower reimbursement. At the risk of oversimplifying the process, the quality scores are based on how well the provider follows a certain predescribed clinical pathway
endorsed by the governing authority (eg, CMS) for the condition at hand. For example, a patient admitted to a hospital during influenza season should be administered an influenza vaccination unless certain deviations are justified. The problem occurs when a provider conducts clinical trials, as you cannot adhere to evidence-based care when you are trying to evaluate new evidence. The provision of investigational care in-and-of-itself or the withholding of evidence-based care for research purposes is incompatible with the evidence-based pathway. The incompatibility between the endorsed treatment protocol and the clinical trial protocol could be the primary intervention itself (eg, the pathway requires radiation therapy for that kind of cancer but the clinical trial is evaluating the use of a drug or device instead of radiation or perhaps evaluating a radiation treatment strategy slightly different than the pathway requires) or a secondary intervention (eg, the clinical trial does not allow beta blockers as a concomitant medication but the clinical pathway requires it).

Fortunately, CMS recognized this and allowed for the exclusion of the clinical trial cases from the denominator of the condition of the measure (ie, a patient on a heart failure clinical trial would not be included in the heart failure denominator but would be included in the influenza vaccination denominator); however, changes to the system have made this impractical. Customarily, to exclude a patient from the denominator, the provider had to have a copy of the signed informed consent document contained within the patient’s medical record and documented sufficiently to show that the study was for the indication of the measure. This means that, in addition to the research files, the full consent document (as the signature page alone was generally not enough to justify that the clinical trial was for the same indication) needed to be scanned into the medical record for the human abstracters to verify the exclusion. As imperfect as that process was, the recent required migration from manual (ie, human reviewed) chart abstraction to electronic abstraction (eCQMs) has caused more significant imperfections. While electronic abstraction theoretically saves time and money and helps prevent human interrater error, the current electronic abstraction method is not smart enough to determine if a clinical trial consent form exists and if it does, if it contains the contextual information necessary to exclude the patient from the denominator of the quality measure. Therefore, the more clinical trials a provider does (and follows the protocol and not the measure’s clinical pathway), the more their quality measures may not reflect the quality actually provided because they cannot exclude those patients from the denominator. As the percentile numbers can sway based on only one or two patients, bringing clinical trials into the ecosystem may be considered too much of a risk (as the online report cards do not explain this anomaly).

5 | MEANINGFUL USE AND OTHER EHR USE INCENTIVES

Since the implementation of the Health Information Technology for Economic and Clinical Health (HITECH) Act in 2009, the ecosystem built offering provider incentives to have “Meaningful Use” of electronic health records (EHRs) has evolved. Based on if the provider meets certain criteria, they are eligible for the Meaningful Use incentives (which originally began as actual incentives in the form of extra payments from CMS and have now evolved to be only disincentives in the form of decreased payments if you are not meeting the criteria for Meaningful Use). It is important to know meeting the Meaningful Use criteria is not based on adopting the software system alone but also based on how the providers use the EHR system. To state this in another way, you can buy/lease an EHR system that is technologically certified for Meaningful Use incentives, but unless you become a meaningful user of that EHR system (also defined by the criteria put forth by CMS and the Office of the National Coordinator for Health Information Technology a.k.a. “ONC”), you will be subject to the disincentives.

As clinical trials are often the proverbial “square peg” in the EHR’s round hole, the more trials a provider undertakes that are either inconsistent or impractically countable towards the Meaningful Use criteria, the more risk the provider takes towards receiving the penalties. CMS’s and ONC’s criteria for Meaningful Use changes from time to time as systems and providers evolve in their adoption. For example, there are past and current criteria regarding how medication ordering is handled (ie, computerized provider order entry or electronic prescribing of hospital discharge medications). Most of these systems utilize existing drug database codes/standards in their infrastructure; therefore, as investigational drugs are not able to be built into the system rapidly and on the fly (i.e. in time for that first medication order), getting the patient what they need outside of the computerized/electronic systems will count against meeting the criteria. The Leapfrog Group that ranks hospitals based on operational criteria also has similar and additional measures (such as the utilization of bar coded medication administration) to which insurers may adjust quality payments on. While the raw numbers of these “square pegs” may be insignificant when compared with the general healthcare setting (especially for a large hospital system), it nevertheless is a marching away from meeting the incentive/disincentive criteria such that providers border lining on these thresholds may take this more seriously than those that are not.

6 | GENERAL BUSINESS AND REGULATORY UNCERTAINTY

There is a subpopulation of patients that migrate towards clinical trials because they are uninsured or underinsured in an effort, in part, to get some care (eg, physical exams and labs) just as there is another subpopulation that migrate away from clinical trials because they are uninsured or underinsured (eg, when the sponsor requires the patient to pay for the routine care affiliated with the study). Similarly, there is a subpopulation that migrate towards clinical trials because they are insured (eg, they hear about the study from their physicians they see regularly and they were able to afford the treatment the trial requires them to have failed first) just as there is a subpopulation that migrate away from trials because they are insured (eg, they prefer treatment over research and they may no longer meet the treatment naïveté requirements of the protocol). As a patient’s insurance status changes, this may also shift those already enrolled (eg, a rising deductible may make the copays and deductibles of the standard-of-care arm no
longer affordable, or perhaps the employer dropped insurance and the patient is now on expanded Medicaid that covers the copays). Needless to say, a patient’s insurance status can affect the recruitment and retention into clinical trials among therapeutic areas (ie, a life-threatening disease versus a more tolerable disease) as well as geography (eg, a major employer in the area shifts insurance plans). The shifting economics of health care payors (eg, retail stores such as CVS and Wal-Mart in talks to buy some of the largest of national insurance companies), health care technologies and personal preferences rapidly shifting locations of care, and the political uncertainty of government programs such as Medicare, Medicaid, and other regulations (eg, the polarizing opinions of the Patient Protection and Affordable Care Act) make it difficult for providers and patients to foresee and plan for the future about their general health care much less what clinical trials to enter. For example, if there is a repeal of the Patient Protection and Affordable Care Act, the Federal requirement of insurance coverage for routine care costs of clinical trials for cancer or other life-threatening conditions (Section 10103) goes away which means that any required clinical coverage reverts back to the states of which about 39 have such requirements (mostly for cancer only).

While the case to diversify payors into a clinical trials portfolio may be made as a result of the above chaos, an educated business choice is offset by several other cases that make the choice to do clinical trials less easy to make. First, clinical trials are typically a small percent of a health care provider’s portfolio thus expending resources to chase that business may be less prudent than focusing elsewhere. Opportunity cost for the space and staff cannot be ignored, especially when this does not introduce a new regulator into their ecosystem (ie, FDA) or challenge their existing regulatory homeostasis with new concepts (eg, mapping records for research use under HIPAA). A busy clinic being asked to dedicate a full-time employee and an office for some clinical trials that may or may not come on time could be offset by hard historical statistics of how many dual energy X-ray absorptiometry (DEXA) scans are sent out each month (where those scans could be done in that space instead if they bought their own machine) or how many genetic counselor referrals went out each month (where that new employee could start with an existing full case load without the need for a more elaborate recruitment, consenting, and retention plans). Finally, the nature of site selection in trials remains for the most part a project-by-project competitive basis, involves an increasingly smaller number of subjects per project, and seems to restart the relationship each time from a contracting and budgeting perspective. If a clinic was running low in volume, chasing and signing up a new insurance plan instead (ie, one contract, one budget negotiation, thousands to tens of thousands more in patient access, payment in <30 days, no holdbacks, no extra paperwork, no monitoring, and no business interrupts) may be a better strategy. If a clinic has a surplus of volume, creating a new access point (eg, a satellite clinic to see the already overflowing patient population without any new payer agreements) may yield better return on investment than trying to cannibalize from the same population (eg, moving a private insurance patient to a study where the sponsor says they cannot pay more than the Medicare rates for the same service). Even with the uncertainty factor stated above, a conservative clinic operator may seek more

stability in the “known unknowns” of the more natural extensions such as in the examples above as opposed to entering into the “unknown unknowns” of the clinical trials business and regulatory structure. Yes, a clinical trial is often touted as “an alternative revenue stream” and "good for patients" and while that may be true, it is not the only alternative revenue stream that is good for patients that a health care delivery system considers on a routine basis.

7 | CONCLUSION

In addition to the steep learning curve of the clinical trial and FDA regulations, there are many additional regulatory and/or accreditation headwinds that are of concern when considering the accommodation of a clinical trial in a health care delivery setting. Only several have been discussed herein but there are other general health care regulations (eg, Stark and Anti-Kickback Laws) and accrediting bodies (eg, The Joint Commission, The Accreditation Association for Ambulatory Health Care) that are tangential to research governance. This is not to say that clinical trials should never be done in a health care delivery setting because they should. This paper attempts to bring clarity to manufacturers, CROs, physicians, and administrators that the challenges, incentives, and disincentives are not isolated to the trial itself. The business decision to attempt the successful implementation of the first trial (and a supporting infrastructure for subsequent trials) is much more complex than it may seem when evaluating the risks, benefits, alternatives, and opportunity costs. It is not good enough that the trial alone be successful in order to continue supporting future trials; the system must benefit as a whole.

Of course, clinical trials are not the only way that health care providers can contribute to the development of drugs, devices, and biologics. In the constant effort to maintain solid science while decreasing cost and time, the FDA continues to evolve in their consideration of “real world evidence” in both the development and post marketing surveillance. FDA has published guidance (and draft guidance) recently such as “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices” (August 31, 2017) and “Use of Electronic Health Record Data in Clinical Investigations” (Draft Guidance Published May 2016) to be included among their many other longer standing initiatives in this area (ie, FDA’s Sentinel Initiative). As these initiatives alter the landscape of how life science can bring in providers that traditionally were not ready, willing, and/or able to accommodate clinical trials, they do bring on their own challenges ... but that is another article for another time.

CONFLICT OF INTEREST

The author affirms that he has no conflict of interest.

How to cite this article: Vulcano D. Tangential headwinds when integrating industry-funded clinical trials into a US health care delivery system. Learn Health Sys. 2019;3:e10075. https://doi.org/10.1002/lrh2.10075