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GUEST EDITOR'S MESSAGE

Norbert Clemens, MD, PhD, CPI

GLOBAL *Regulatory Insights*

Clinical research for both pharmaceuticals and medical devices on a global scale is an area of high complexity. This includes the respective regulations, local laws, and guidance documents that have been developed over the last few decades.

Furthermore, the trend of offshoring clinical trials from the initial regions of the International Conference on Harmonization (ICH) toward other regions within developing countries is ongoing. This is due to the fact that it is increasingly recognized in the U.S., Europe, and Japan that trials have become too expensive and bureaucratic. For pharmaceutical and medical device companies, the benefits of conducting trials in emerging regions include lower overall development cost, faster timelines, and increased patient populations. In addition, global clinical trials potentially lead to simultaneous marketing authorizations of new medical entities in multiple regions of the world.

A great portion of clinical trials is shifting to BRICS countries—that is, the association of five major emerging national economies: Brazil, Russia, India, China, and South Africa—four of which are covered in this issue.

The importance of well-regulated clinical trials to ensure high ethical standards as well as trial conduct and processes resulting in valid and accurate data must be emphasized. However, many stakeholders advocate for making trial regulation less complicated and more readily adaptable to risk, and for having guidelines that are globally applicable. Moreover, regulations and laws dealing with clinical trials are continuously being modified and updated. Therefore, the Editorial Advisory Board of *Clinical Researcher* decided to focus on regulatory updates in this issue. We were able to attract expert authors from around the world to contribute to this topic.

To read our Article Submission Guidelines, see page 81.

As the Ebola epidemic is still a hot topic, we appreciate the opportunity to present a thought-provoking opinion paper by Dr. Philip Rosoff dealing with departures from ethical standards in cases involving desperation. Dr. Rosoff is director of the Clinical Ethics Program at Duke University Hospital and a professor of pediatrics. He recently published his first book, *Rationing is Not a Four-Letter Word: Setting Limits on Healthcare,* published by MIT Press.

The South African National Clinical Trial Register currently covers more than 1,900 registered trials. Suheila Abdul-Karrim, head of the ACRP South Africa Chapter, provides an update on progress in clinical research linked to 20 years of democracy in her country. Over the past decade, South Africa has become an important destination for many international pharmaceutical companies looking to conduct clinical trials.

Dr. Gustavo Kesselring and his coauthors elaborate on clinical trial approval delays in Brazil, the largest country in Latin America. Dr. Kesselring is the current president of the International Federation of Associations of Pharmaceutical Physicians & Pharmaceutical Medicine. He received an Honorary Lifetime Membership Award from the ACRP affiliate now known as the Academy of Physicians in Clinical Research in 2011.

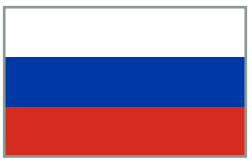
Clinical research in India using shortcuts that result in ethics violations has been a hot topic since 2012. Purviben Trivedi-Ziemba shares a current update on the regulatory environment that might negatively affect clinical research in India. Rebuilding trust in the ability to conduct clinical research in India will need efforts from investigators, ethics committees, and sponsors.

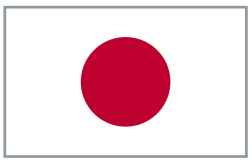
The Russian perspective has been compiled by Dr. Elena Storozhuk and her colleague, Dr. Svetlana Cherdantseva. Their paper explains the federal law "On circulation of medicines" and the resulting changes following its implementation in 2010.

In September 2012, an article in *The Monitor* focused on the Middle East and North Africa (MENA) region. This time we have put the spotlight on Jordan, one of the leading countries in this area. Emad Shafout reviews the current status and areas of improvement for clinical trials in Jordan.

Clinical trials include Phase IV studies, which are usually conducted to clarify further safety







questions. Sometimes these trials are conducted for different purposes, as the article from Chieko Kurihara shows. She describes lessons learned from a scandal in Japan involving valsartan (better known as Diovan®). In addition, her article compares regulations for Phase IV studies in the different initial ICH regions.

At the beginning of this editorial, I mentioned medical devices as an important part of the clinical research arena. Glenda Guest addresses the question whether the Global Unique Device Identification Database (GUDID) is a GOOD IDea. Besides premarket implications, the medical device adverse event surveillance is in the focus of her article.

Finally, Regina Freunscht and I explore the administrative and operational changes of the new European Clinical Trial Regulation, which was published in May 2014. Regulations are the most direct form of European Union law; as soon as they are passed/published, they have binding legal force throughout each of the 28 member states, on a par with national laws. The regulation is expected to come into force around 2016, and is supposed to increase the speed of clinical research within the European Union.

The last article completes the "World Tour" on regulations for clinical research, which covered the initial ICH regions as well as 80% of the BRICS countries. We hope you enjoy the journey by reading this issue's global coverage of regulatory issues.

Norbert Clemens, MD, PhD, CPI, (nclemens@email.de) is managing director and head of clinical development at CRS Mannheim GmbH in Gruenstadt, Germany. He serves on the ACRP Editorial Advisory Board as well as the Executive, Finance, Governance, Executive Director Performance and Compensation committees. He is the elected Vice Chair of the ACRP Board of Trustees (ABoT) and also serves as the ABoT Liaison to the ACRP Global Conference Planning Committee.

BY THE NUMBERS

Summing up recent facts and figures influencing the communications/promotions side of drug and device development.

When considering platforms to use, patient recruiters should be aware that Facebook accounts for 34% of all social media traffic, Twitter for 4%, and LinkedIn for just 1%.

34%

4%

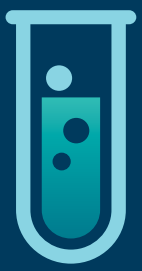
1%

Source: Promotional spot for the "5 Proven Secrets of Social Media Success for Patient Recruitment" webinar, http://app.caerusmarketing.com/2-best-social-media-platform-for-patient-recruitment

49% of drug development services say their companies use both internal and outsourced services to meet their marketing goals,

50% say they have a social media strategy.

Source: "2014 Marketing Trends in Drug Development Services" from SCORR Marketing, www.scorrmarketing.com



There are **771** new medicines in development to fight cancer—up to **80%** of which have the potential to be first-in-class medicines.

Source: "Researching Cancer Medicines: Setbacks and Stepping Stones" from PhRMA, www.phrma.org

One CRO-formulated communication and recruitment strategy using ads in public transit systems and text message alerts led to **138 healthy volunteers** being enrolled within **13 days** for a client's early-phase study, helping reduce overall time for postclinical services by **8 weeks.**

Source: "Clinical Research: A Legacy of Innovation, A Future of Transformed Medicine" from the Association of Clinical Research Organizations, www.acrohealth.org

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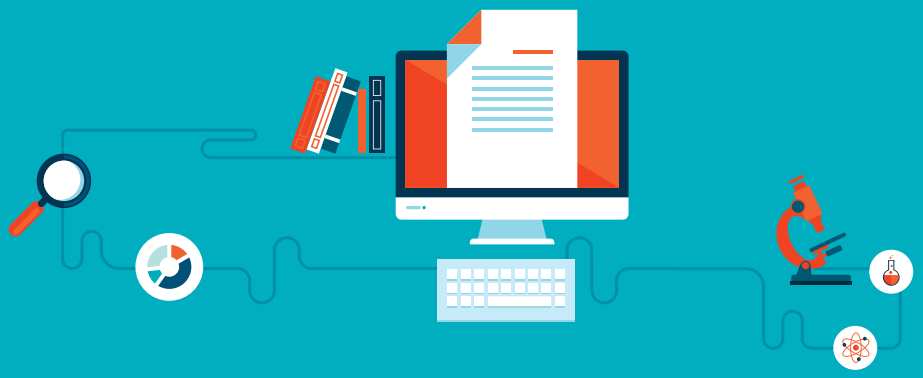
Suzanne M. Heske, RPh, MS, CCRA, BCNP



Telling the Clinical Trial Regulatory Story: CRAs Have a Role

Can the investigator site staff or sponsor tell the clinical trial story from beginning to end using the existing essential documents (e.g., site regulatory binder in paper and electronic version)? Whether by a novice or experienced clinical research associate (CRA), review of investigator site regulatory documents is a necessary task. Yet this crucial element of the story often goes unnoticed or gets postponed due to a myriad of competing demands.

The keys to compiling and maintaining essential documents are organization and consistency.

A clinical trial story should consist of pages of essential documents or trial master file (TMF)—those which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. The control and maintenance of essential documents is not only a regulatory expectation, it provides sponsors, investigators, CRAs, and institutional review boards (IRBs) assurance of compliance.

Furthermore, appropriate control of essential documents falls under the guidelines of good clinical practice (GCP) and serves as a unified standard for the European Union (EU), Japan, United States, and other countries for all clinical trials. The International Conference on Harmonization (ICH) Guidance for Industry (E6 GCP Part 8) spells out the minimum document retention requirements for each of the three critical phases of a clinical trial: pre-study, during the study, and post-study.

Establishing the Process

The keys to compiling and maintaining essential documents are organization and consistency. GCP does not provide guidance on how to organize essential documents, so creating a systematic method of organization that works best for everyone is crucial. Generally, the organizational structure is dictated by sponsors' policies and procedures, but there is room for CRAs to employ individual tools and techniques.

Consideration should also be given to how (i.e., categorizing based on hierarchy) and where documents will be maintained (paper-based or electronically; original or copy). Once established, this process must be consistently maintained throughout the conduct of each trial. Understanding the purpose for each document and knowing whether it should be filed in either the investigator/institution or sponsor files, or both, will help ensure consistency.

The regulatory files/binder/TMF should be in place at the beginning of the trial, both at the investigator/institution's site and at the sponsor's location. The bulk of regulatory documents are created before the actual clinical phase of a trial begins and should be continuously maintained, updated, and controlled throughout the course of the study, and retained or archived for a sufficient period after the study. CRAs need to be knowledgeable of the content and quality of these documents, including when implemented, approved, amended, and considered final, to ensure they reach the appropriate file(s). The essential documents listed in Table 1 (not all inclusive) are some of the highest priority documents. The notes section calls out additional details where CRAs often have questions.

Telling the Story

Each chapter of the story needs to be reflected through essential documents. It's probable that sponsors/sites maintain chapters of their story in multiple locations and not just a regulatory binder or TMF. Review of all chapters including the regulatory binder should be routinely performed by CRAs and others to ensure quality and completeness.

What is your site's story?

Suzanne M. Heske, RPh, MS, CCRA, BCNP, (suzanne.heske@inventivhealth.com) is associate director for operational quality management with inVentiv Health Clinical.

TABLE 1: Essential Documents (Based on ICH GCP Guidelines – E6)

Essential Documents	Pre-Study	During Study	Post-Study	Notes / CRA Tips
Investigator Brochure	✓	✓		Investigational drug brochure and safety package insert are required for each U.S. Food and Drug Administration (FDA)-approved agent. CRA to confirm if investigator signature page is required and original is on file.
Signed protocol and amendments, and sample case report forms (CRFs)	✓	✓		
Information given to trial subject	✓	✓		Informed consent form (ICF), translations, accents, and other written information to support ability to consent, and advertising for subject recruitment. CRAs to confirm all versions are retained in site file (current/historical). Suggest site maintain outdated documents in separate binder labeled as such, so outdated or unapproved version is not accidentally used.
Dated, documented favorable opinion of IRB or independent ethics committee (IEC)	✓	✓		Protocol (signed), amendments, ICF, written subject information, compensation, advertisements for recruitment, and other written information.
IRB/IEC composition	✓	✓		CRA to confirm all versions are maintained throughout the life of the study. Outdated version may be kept in a separate location with a note in the current site binder identifying where past versions are being housed.
Regulatory Authority authorization/ approval/notification of protocol	✓	✓		
FDA Form 1572	✓	✓		Investigator's agreement to conduct trial according to the obligations stated in the form is required for all new drug trials, but not required for all studies. CRAs to ensure all signed versions provided to the sponsor (historical/current) reconcile with those retained in the site file.
Delegation of authority (DOA) log	✓	✓		Complete with names and titles of all staff delegated responsibility for protocol-related tasks. Identifies the training that qualifies staff to perform the delegated tasks and the dates of staff involvement. Suggest CRAs routinely (at every visit) reconcile the DOA with site team members to ensure tasks are being performed by appropriately delegated staff and to address changes in personnel.
Curriculum vitae or other relevant document evidencing qualifications	✓	✓		Education, training, and experience of investigators and sub-investigators (i.e., evidence of GCP training).
Financial aspects of trial/agreement between all involved parties	✓			Financial disclosures and confidentiality agreement regarding the investigator and the manufacturer of the product being studied. Clinical trial agreement is the legally binding agreement that is not regulated by or disclosable to FDA. Sponsor transfer of obligations/responsibilities to contract research organizations (CROs). CRAs generally are not responsible for reviewing the clinical trial agreement, but should confirm the document's location separate from the regulatory binder.
Insurance statement (where required)	✓			Documents related to subject(s) compensation for trial-related injury will be available (i.e., Certificate of Assurance or Indemnification).
Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol.	✓	✓		Certifications, accreditations, established quality control and/or external quality assurance or other validation where required. CRAs to routinely reconcile and collect updated certificates/values to ensure data reflect current normal ranges.
Investigational product (IP) shipping/handling records	✓	✓	✓	Batch/lot numbers, distribution dates, methods, and conditions of distribution and accountability and sample of label. At time of trial termination, final IP accountability to confirm use in accordance with the protocol includes the following documentation: IP received at each site, dispensed to subjects, returned by subjects and to the sponsor, destroyed by the site.
IP Certificate of Analysis	✓			
Decoding procedures for blinded trials	✓			
Master randomization list	✓			CRAs should ensure the site maintains a master randomization or subject ID assignment log, which provides a verifiable link between subject ID and treatment assignment.
Monitoring reports	✓	✓		Reports at each phase of a trial: pretrial—suitable to conduct trial, trial initiation—demonstrates protocol requirements were review- and site-trained, regular monitoring visit reports document findings, compliance, etc., final closeout—confirms essential documents are completed and present, including location where records will be maintained, disposition of subjects, specimens, and study drugs, and IRB notification of study termination with final report. CRAs to confirm all monitoring visit reports are maintained with the sponsor or CRO and ensure all correspondence (e.g., confirmation and follow-up letters) is filed in the site binder and is reconciled with sponsor files.
Documentation of relevant communications		✓		Letters, meeting notes, notes of phone or e-mail communications, information reported to the IRB, sponsor, or regulatory authorities.
Signed ICF and patient privacy forms		✓		Geographically specific patient privacy forms (e.g., Health Insurance Portability and Accountability Act form in the U.S.). CRAs to confirm subjects sign the appropriate version per the IRB approval letter(s) and the site retains copies of all signed ICFs for all subjects.
Source documents		✓		
Signed, dated, and completed CRFs		✓		Documentation of CRF corrections.
Protocol deviation/violation logs		✓		CRA to confirm IRB notification and correspondence are filed within the site binder.
Serious adverse event notification		✓		Reports and/or safety information submitted to sponsor and/or IRB.

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The intent of this policy is not to prevent individuals with relevant financial relationships from participating; it is intended that such relationships be identified openly so that the audience may form their own judgments about the presentation and the presence of commercial bias with full disclosure of the facts. It remains for the audience to determine whether an individual's outside interests may reflect a possible bias in either the exposition or the conclusions presented.

80% The pass rate for the Home Study Test is now 80% to be in alignment with ACRP professional development standards.

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Is the GUDID a GOOD IDea?

Can Unique Device Identification (UDI) and Global UDI Database (GUDID) Improve Medical Device Development and Surveillance?

PEER REVIEWED | Glenda Guest, CCRA, RQAP-GCP

[DOI: 10.14524/CR-14-0031]

LEARNING OBJECTIVE
After reading this article, participants should be able to discuss possible improvements in several areas for devices (for example, safety signals) through the FDA requirements for UDI/GUDID.

DISCLOSURES
Glenda Guest, CCRA, RQAP-GCP: *Employee of, and major stockholder in, Norwich Clinical Research Associates*

It is well known that there are limitations to our assessment of safety and effectiveness of medical products due to the nature of clinical research. For example, clinical studies, when required, are designed to support safety and efficacy claims based upon data that have been gathered from only a subset of the potential patient pool for the product.

We design studies to limit the exposure of subjects to those who will most likely demonstrate a benefit from having used the product, while reducing the risks of exposure by the inclusion and exclusion criteria stipulated in our study protocols. Once a product has been assessed and either cleared or approved for market, the limitations of the clinical trial environment no longer apply.

Therefore, it is in this postmarket environment that we are most likely to see the benefits of unique device identification (UDI) reporting. Previously unobserved, or low frequency, events may now be more accurately reported, so trends can be identified earlier and addressed as appropriate.

Provided next, an overview of past practices regarding medical device adverse event surveillance may help make this point more clearly.

Background

Over time, there have been several different methods for capturing postmarket medical device safety data in the U.S. The current regulation on Medical Device Reports (MDRs) found in the *Code of Federal Regulations* (21 CFR 803)[1] contains mandatory requirements for manufacturers, importers, and device user facilities to report certain device-related adverse events and product problems to the U.S. Food and Drug Administration (FDA). The regulation specifies that reports be filed on FDA MedWatch Form 3500A or an electronic equivalent. The FDA published a final rule[2] on February 14, 2014, requiring manufacturers and importers to submit MDRs to the FDA in an electronic format that the FDA can process, review, and archive. At the time of this writing, this rule was to become effective on August 14, 2015.

Information on the requirements for each mandatory reporting group follows.

- **Manufacturers** are required to report to the FDA when they learn that any of their devices may have caused or contributed to a death or serious injury (key terms are defined in 21 CFR 803.3[3]). Manufacturers must also report to the FDA when they become aware that their device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.
- **Importers** are required to report to the FDA and the manufacturer when they learn that one of their devices may have caused or contributed to a death or serious injury. The importer must report only to the manufacturer if its imported devices have malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.[4]
- **Patients and providers?** The FDA encourages healthcare professionals, patients, caregivers, and consumers to submit *voluntary* reports of significant adverse events or product problems with medical products to MedWatch, the FDA's Safety Information and Adverse Event Reporting Program, which is not specific to medical devices.

The Manufacturer and User Facility Device Experience (MAUDE) database contains mandatory reports filed by manufacturers and importers from August 1996 to the present, all mandatory user facility reports from 1991 to the present, and voluntary reports filed after June 1993. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as healthcare professionals, patients, and consumers.

Noting that an event would require the manufacturer to provide an MDR report, and yet the same event could also be voluntarily reported via MedWatch by the healthcare professional and the patient, for example, highlights one of the challenges in effective use of the available device safety reporting information.

It is worth mentioning that FDA has plans to replace the MAUDE database with a newer system called Pharmacovigilance Report Intake and Managed Output (PRIMO). FDA is unable to leverage MAUDE's capabilities to conduct real-time reporting and analysis, slowing any attempts to discover unknown adverse events. This, in turn, affects its ability to generate and evaluate evidence.

In a press statement released in September 2013, the November Research Group said it had won an FDA contract to have its PRIMO software system eventually replace MAUDE.[5]

Scope and Limitations of Reporting

Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries, and malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products.

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone, due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources.

Among the concerns about MDRs are the following:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified, or if the device in question has not been directly evaluated.

It is in this postmarket environment that we are most likely to see the benefits of unique device identification (UDI) reporting. Previously unobserved, or low frequency, events may now be more accurately reported, so trends can be identified earlier and addressed as appropriate.

TABLE 1: Summary of Compliance Dates for the UDI Final Rule[7]

Compliance Date	Requirement
One year after publication of the final rule (September 24, 2014)	Labels and packages of Class III medical devices and devices licensed under the Public Health Services Act (PHS Act) must bear a UDI. § 801.20 Dates on the labels of these devices must be formatted as required by § 801.18. Data for these devices must be submitted to the GUDID database. § 830.300 A one-year extension of this compliance date may be requested under § 801.55; such a request must be submitted no later than June 23, 2014. Class III standalone software must provide its UDI as required by § 801.50(b).
Two years after publication of the final rule (September 24, 2015)	Labels and packages of implantable, life-supporting, and life-sustaining devices must bear a UDI. § 801.20 Dates on the labels of these devices must be formatted as required by § 801.18. A life-supporting or life-sustaining device that is required to be labeled with a UDI must bear a UDI as a permanent marking on the device itself if the device is intended to be used more than once and intended to be reprocessed before each use. § 801.45 Standalone software that is a life-supporting or life-sustaining device must provide its UDI as required by § 801.50(b). Data for implantable, life-supporting, and life-sustaining devices that are required to be labeled with a UDI must be submitted for the GUDID database. § 830.300
Three years after publication of the final rule (September 24, 2016)	Class III devices required to be labeled with a UDI must bear a UDI as a permanent marking on the device itself if the device is intended to be used more than once and intended to be reprocessed before each use. § 801.45 Labels and packages of Class II medical devices must bear a UDI. § 801.20 Dates on the labels of these devices must be formatted as required by § 801.18. Class II standalone software must provide its UDI as required by § 801.50(b). Data for Class II devices that are required to be labeled with a UDI must be submitted for the GUDID database. § 830.300
Five years after publication of the final rule (September 24, 2018)	Class II devices required to be labeled with a UDI must bear a UDI as a permanent marking on the device itself if the device is intended to be used more than once and intended to be reprocessed before each use. § 801.45 Labels and packages of Class I medical devices and devices that have not been classified into Class I, Class II, or Class III must bear a UDI. § 801.20 Dates on the labels of all devices, including devices that have been excepted from UDI labeling requirements, must be formatted as required by § 801.18. Data for Class I devices and devices that have not been classified into Class I, Class II, or Class III that are required to be labeled with a UDI must be submitted for the GUDID database. § 830.300 Class I standalone software must provide its UDI as required by § 801.50(b).
Seven years after publication of the final rule (September 24, 2020)	Class I devices and devices that have not been classified into Class I, Class II, or Class III that are required to be labeled with a UDI must bear a UDI as a permanent marking on the device itself if the device is intended to be used more than once and intended to be reprocessed before each use. § 801.45

NOTE: Compliance dates for all other provisions of the final rule. Except for the provisions listed above, FDA requires full compliance with the final rule as of the effective date that applies to the provision.

- The data from the MAUDE database do not represent all known safety information for a reported medical device, and should be interpreted in the context of other available information when making device-related or treatment decisions.
- Variations in trade, product, and company names affect search results. Searches only retrieve records that contain the search term(s) provided by the requester.
- Submission of an MDR and the FDA's release of that information are not necessarily an admission that a product, user facility, importer, distributor, manufacturer, or medical personnel caused or contributed to the event.[6]

Adding to the potential unreliability of data in these voluntary and mandatory reporting systems is the fact that there is a potential for duplicate reporting when a medical device is available on the market for one approved indication and is being studied for a new indication or claim. These situations have requirements for reporting serious and unexpected adverse device events (UADEs) to FDA as part of an ongoing Investigational Device Exemption, but that same information must also be reported as an MDR because of the marketed status of the device. The ability to trace the serious UADEs to a UDI may be beneficial in eliminating this potential duplication of reporting (see Figure 1 for an example of the appearance of a UDI).

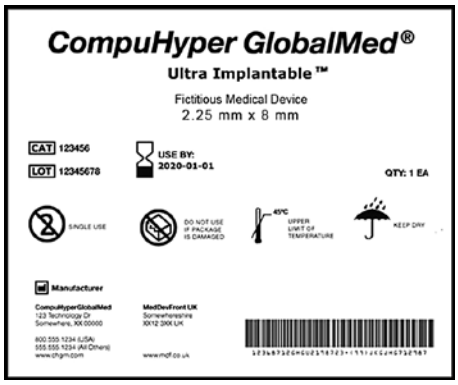
Improving Upon the Situation

It becomes apparent that improvements are needed to foster faster and more reliable reporting and sharing of unexpected and serious adverse events related to medical devices. FDA has outlined implementation of the UDI requirements as a "phased" approach, with requirements for compliance dependent upon the risk of the device (see Table 1).

When fully implemented, the UDI system can:

- Allow more accurate reporting, reviewing, and analyzing of adverse event reports, so that problem devices can be identified and corrected more quickly.
- Reduce medical errors by enabling healthcare professionals and others to more rapidly and precisely identify a device and obtain important information concerning its characteristics.

FIGURE 1: Example of the Appearance of a UDI



- Enhance analysis of devices on the market by providing a standard and clear way to document device use in electronic health records, clinical information systems, claims data sources, and registries. A more robust postmarket surveillance system can also be leveraged to support premarket approval or clearance of new devices and new uses of currently marketed devices.
- Provide a standardized identifier that will allow manufacturers, distributors, and healthcare facilities to more effectively manage medical device recalls.
- Provide a foundation for a global, secure distribution chain, helping to address counterfeiting and diversion and prepare for medical emergencies.
- Lead to the development of a medical device identification system that is recognized around the world.

In short, the UDI system has the potential to improve the quality of information in medical device adverse event reports, which will help the FDA identify product problems more quickly, better target recalls, and improve patient safety.[7]

While MDR reporting continues to include both the mandatory and voluntary reporting systems now in place, the UDI final rule:[8]

> is expected to substantially reduce existing obstacles to the adequate identification of medical devices used in the United States. By making it possible to rapidly and definitively identify a device and key attributes that affect its safe and effective use, the rule will reduce medical errors that result from misidentification of a device or confusion concerning its appropriate use. The identification system established under this rule will lead to more accurate reporting of adverse events by making it easier to identify the device prior to submitting a report. It will allow FDA, healthcare providers, and industry to more rapidly extract useful information from adverse event reports, pinpoint the particular device at issue and thereby gain a better understanding of the underlying problems, and take appropriate, better-focused, corrective action.

Conclusion

The limitations inherent in the premarket review and clearance/approval for marketing of devices, and the pitfalls and shortcomings of our current surveillance systems, make clear that FDA's requirements for UDI and GUDID offer the hope of improvements in a number of areas, not the least of which is the potential for faster identification of safety trends or signals. However, in an era of "big data" and FDA's more recent initiatives to balance premarket and postmarket data in efforts to foster innovation, speed to market will also be dependent on the availability of this type of data.[9] It seems to me to be a very GOOD IDea.

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Clinical Research in India

PEER REVIEWED
Purviben Trivedi-Ziemba, BS, MEd
[DOI: 10.14524/CR-14-0032]

Clinical research has developed into an industry operating on an international scale. Such development has been preceded by scientific and business interest. On the scientific side, the design of studies with large sample sizes and diverse populations has led to a need to globalize. However, the argument could be made that business needs have been a greater force when running either multinational studies or studies focused in regions of the world that were not as readily accessible only decade ago.

The opening of markets in areas as varied as Asia, Russia, Eastern Europe, Latin America, and Africa have led to a multitude of opportunities not only to bring the opportunity of clinical research to these areas, but also to access potentially larger and diverse study populations. Each of these markets has nevertheless presented the clinical research enterprise with challenges in one way or another. Among them, India has presented itself not only as a land of great opportunity for both the scientific and business aspects of clinical research, but also as a challenging environment in which to conduct studies.

This article explores some of the reasons for conducting clinical research in the Indian market, the issues that have occurred, and the regulatory reaction.

LEARNING OBJECTIVE
After reading this article, participants should be able to construct an informed analysis of how the concerns and resulting actions indicate that the Indian market is a viable location for clinical research.

DISCLOSURES
Purviben Trivedi-Ziemba, BS, MEd: *Nothing to Disclose*

Background

India presents several advantages for the conduct of clinical trials. Its greatest resource is its population, contributing both a huge patient population and one that is genetically diverse.[1] It also presents a large talent pool that can handle all aspects of preclinical and clinical studies, from researchers engaged in molecular discovery and statisticians engaged in study design to research staff, especially physician investigators.

The Indian clinical research industry expanded greatly during the 1990s and 2000s, leading to a multitude of outsourced services, such as those tied to translation and contract research organizations.[2] However, with the United States as the largest market for drugs, biologics, and medical devices, the need to take advantage of this market is obvious.

One consideration is the practice of the U.S. Food and Drug Administration not to approve data from trials when greater than 20% of the study subjects were derived from developing countries, like India. Despite this barrier, India's clinical trials industry thrived, up to a point, because a wealth of resources and expertise were available, and because the cost of conducting clinical trials there has been estimated to be 60% of conducting the same trial in the U.S. Thus, a savings can still be realized, even if only a portion of the study sample is derived from India.

The Consequences of Rapid Growth

The rapid onset of clinical trials into India has not been without its consequences, as accusations of unethical behavior among study investigators and sponsors recently built to a level that affected research on a national scale. Of special note, a number of alleged allegations of ethics violations in the state of Madhya Pradesh led to concerns and a loss of trust over the conduct of research in the country as a whole.[3]

An example of these violations, which were highlighted by an activist group, is seen at a public hospital in the city of Indore, where a total of 3,300 patients (approximately half of them children) were placed in clinical trials. Of these, 81 patients experienced severe adverse events and death. A subsequent investigation found that the informed consent that was conducted was poor, including consenting non-English–speaking patients with English consent documents. Also, there was little to no compensation for injuries. Allegations of a cover-up followed, as the physicians involved were fined only 5,000 rupees ($100) each.

The large sums of money paid by pharmaceutical companies to conduct trials and the occurrence of apparent serious events and ethics violations with little in the way of punishment led to activism, resulting in the banning of new trials in Madhya Pradesh in 2010. Further, this was not an isolated incident, which led some observers to conclude that the Indian clinical trials market grew too rapidly for effective regulation, making it easy for violations to occur.

Other examples of violations have been publicized, including the suggestion by a government officer that the warden for a girls' hostel could authorize the involvement of the girls in a clinical trial for a cervical cancer vaccine without parental permission, and the exposure that ethics committees were not operating independently of investigators.[4]

Sweeping Actions for Reform

Actions taken since the occurrences of violations have been extensive and encompassed the highest levels of the federal government. The Indian Supreme Court banned the opening of studies in 2013 across the country until adequate resolutions were in place. This action effectively derailed an industry worth more than $450 million and with an expected annual growth rate of 12% in 2010–11.

Much of the focus was placed on how the government approved studies, and the shortcomings highlighted in this process bolstered the shutdown of trials until the government could provide a plan for effective oversight. In the short time period since, certain sweeping actions toward rehabilitation have indeed been taken, which point to the seriousness of the issues at hand—at least to the extent that these issues are widely known.

Certainly, publicity surrounding the deaths of clinical trial participants and a lack of compensation for research-related injury in widely read news media, such as the *Times of India,* contributed to the reaction of the Supreme Court. Regardless, the potential extent of the ethics issues required drastic action. Emphasis has been placed on

India has presented itself not only as a land of great opportunity for both the scientific and business aspects of clinical research, but also as a challenging environment in which to conduct studies.

A concerted effort among investigators, sponsors, ethics committees, and other research professionals is needed to rebuild trust in India's ability to engage in clinical research and demonstrate that India is open for the clinical research business.

making the conduct of clinical trials more transparent, including changes in the consent process, medical management, and financial compensation for trial-related injury.[5]

Audio-Visual Informed Consent

Perhaps one of the more visible steps taken occurred shortly after the Supreme Court action, and addressed the documentation of informed consent. The Drug Controller General of India (DCGI) mandated in November 2013 that, in addition to written consent, investigators would need to conduct audio-visual recording of the informed consent process of each individual enrolled to a clinical trial and to keep these records on hand.

However, this approach has met with criticism, most notably from investigators, institutional review boards, and trial managers.[6] One proposal suggests, in addition to creating a record of the consent process, the act of audio-visual recording will increase compliance. However, its potential disadvantages include expense, refusal of subjects to be recorded, and risk to confidentiality.

Little is known, however, about the effects, or effectiveness, of audio-visual recording of the informed consent process. It may provide a mechanism to demonstrate effectively that a subject was consented in a compliant manner. Alternatively, it may prove to be a deterrent to enrollment.

Medical Management

Meanwhile, the medical management of patients participating in clinical trials and their compensation were strengthened to place more responsibility on the investigator and sponsor.[5] The draft guidelines address three areas:

- Provision of free medical care for any injury occurring during a clinical trial, until it can be determined that the injury is not related to the trial. This guideline places onus on the investigator, as emphasis is on patient care with no charge to the patient, prior to any determination of whether the injury was related to the clinical trial. The determination of the nature of the injury is likely up to the investigator.
- Payment of compensation by the sponsor if the injury is trial related. A clarification states that no compensation will be made if the investigational agent does not have its desired effect or does not have any other benefit.
- Stipulation that any case of injury to or death of a patient on a trial's placebo arm is eligible for compensation only if standard-of-care was not provided.

These guidelines apparently attempt to strike a middle ground, by providing for protection of the clinical trial patient, while not placing all the pressure on the investigator or sponsor. Patient care does come first; however, the guidelines allow for the possibility that any injury sustained by the patient may not be related to the clinical trial.

Trial Registry to the Rescue?

Another dramatic development involves the implementation of a clinical trial registry. The Clinical Trials Registry—India (CTRI) is a database of in-depth information, submitted online, on clinical trials.[7] The chart summarizes the data collected.

The purpose of the registry is to provide the public with information on clinical trials, while inhibiting compliance violations and the nonreporting of negative trial results in an environment where a number of ethics committees, investigative sites, and journals require that a trial be registered. However, challenges regarding compliance with registration and the quality of the entered information have been encountered.[8] An interesting finding since implementation of the registry is the much more accurate reporting of study methodologies for registered trials, as opposed to earlier methodologies reported for published studies.[9]

The Indian Researchers' View on Ethics

The impact of the various protective measures taken in India has been dramatic, resulting in the suspension of the country's research industry and subsequent loss of economic benefits. However, little has been done to subjectively investigate how Indian clinical research professionals view research ethics in their own country.

A survey of clinical research professionals in India attempted to answer this question.[10] A total of 500 surveys were distributed, presenting 12 questions on identification of top ethical issues, independence of ethics committees, and adequacy

of the informed consent process, among other topics. Unfortunately, only 34 surveys were returned, negating statistical significance; however, the results obtained still provide a telling review. Table 1 provides a summarization of some of the published results.

TABLE 1: Clinical Research Professionals' Opinions on Ethics in India[10]

Item	Result
Top three issues	Informed consent process Empowerment of ethics committees Patient awareness of safety
Independence	Ethics committees do not operate independently
Informed consent process	Subjects are not adequately informed Risks are not explained adequately The need to record is explained Alternatives are presented Patients can refuse participation

The results indicate positive aspects (recording is explained, alternatives to trial participation are presented) and negative aspects (an inadequate informed consent process, ethics committees not operating independently). A study such as this does not explain the entire industry—not only because of the low response rate, but those who answered the survey may also be more likely to pay attention to ethical factors.

However, the fact that the study was conducted does demonstrate that clinical research ethical measures are setting a precedent in India. Not only are actions being taken, but evidence exists that the actions are being taken seriously.

Conclusion

India presents a vast market for clinical research. Its large population of treatment-naïve patients, its extensive medical expertise among physicians and researchers, and its leaders' strong desire to see the nation participate fully in global clinical research present a country that can compete internationally. However, as in other parts of the world, attention to the education of investigators and clinical research professionals and to protective measures is needed to ensure the safety and wellbeing of participants in clinical trials.

The regulations that have been passed are in reaction to ethics violations that have occurred. These incidents damaged trust in the clinical research industry of India, and may have cast a shadow on clinical research worldwide. Intervention is needed; however, overly excessive regulation can also stifle the industry.

A concerted effort among investigators, sponsors, ethics committees, and other research professionals is needed to rebuild trust in India's ability to engage in clinical research and demonstrate that India is open for the clinical research business.

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CTRI DATA POINTS ON CLINICAL TRIALS

- Public title of study
- Condition studied
- Scientific title of study and its acronym
- Study type
- Secondary or alternate identification numbers
- Agents (intervention and comparator)
- Principal investigator name and address
- Inclusion/exclusion criteria
- Contact person (scientific query)
- Method of randomization
- Contact person (public query)
- Method of allocation concealment
- Sources of monetary support
- Blinding/masking
- Primary sponsor
- Primary and secondary outcomes
- Secondary sponsor
- Target sample size
- Countries of recruitment
- Phase of trial
- Sites of study
- Date of first enrollment
- Name of ethics committee
- Estimated duration of trial
- Approval status
- Recruitment status
- Regulatory clearance from DCGI
- Brief summary

Adapted from www.ctri.nic.in

The "On Circulation of Medicines" Law in Russia: *Four Years Later*

PEER REVIEWED | Elena Storozhuk, MD, MS | Svetlana Cherdantseva, MD, PhD

[DOI: 10.14524/CR-14-0034]

The federal law "On circulation of medicines"[1] went into effect in 2010 in the Russian Federation. As a result, significant modifications in the regulatory framework and structure were made in support of the lawmakers' attempt to create a more structured and clearly defined setting for clinical trial conduct in Russia.

LEARNING OBJECTIVE
After reading this article, participants should be able to describe the impact of the "On circulation of medicines" law in Russia, the new bill introducing changes in the current law, and compare the European Union and Russian legislation on clinical trials.

DISCLOSURES
Elena Storozhuk, MD, MS; Svetlana Cherdantseva, MD, PhD: *Nothing to Disclose*

The law distinguishes between trials that could be conducted regardless of subsequent registration of medicine in Russia (international multicenter clinical trials, post-registration trials, and bioequivalence trials), and provides guidance for trials that would be conducted within the framework of the registration process (marketing authorization). It also describes a process for registering medicines in Russia, including the conduct of clinical trials to support the registration dossier.

Among other points, the law depicts the review process and timelines for obtaining study approvals for any type of interventional clinical studies; modifies insurance coverage in clinical trials; and toughens the requirements for investigative sites and principal investigators participating in interventional clinical research for novel chemical and biological entities.

As soon as "On circulation of medicines" was implemented in April 2010, it became a target for wide discussion and criticism within the research community of Russia. At the beginning, many stakeholders within Russia shared an overall positive view of the changes triggered by the implementation of the new law. The potential attractiveness was based on an expectation of a well-defined pathway that could have been referenced for any clinical development program and shortened review timelines.

However, it became obvious that some of the proposed changes made the registration process in Russia even more challenging. There was a pressing exigency to change some of the requirements and guidelines in a new law, in order to address the needs of biopharmaceutical and generic companies working in Russia.

As a result of discussion and collaboration among the Ministry of Health, federal agencies, and different representatives of the pharmaceutical market, a new bill—"On introducing the changes into 'On circulation of medicines'"[2]—was developed, and is expected to become effective in January 2015. The bill, which is properly seen as an addendum to additional guidance, focuses

primarily on the issues of registration and regulation of medicinal products, including marketed and investigational drugs.

In spite of several positive aspects, the new bill seems to have multiple problematic issues, requiring further improvements. A comparison of regulation in effect within the European Union (EU) to that now implemented in Russia provides context for interpreting the impact of this legislation.

Changes Following Implementation of "On Circulation of Medicines"

Market Structure

Although there are no data suggesting that the new law has enhanced data integrity, its implementation has led to noteworthy changes in the clinical trials market in the Russian Federation in terms of interest in, approval of, and initiation of studies.

Immediately following the introduction of the new law and reforms to the clinical trial approval system in 2010, the total number of trial approvals decreased, reflecting uncertainty in interpretation of new guidance. It took a year for the market to recover, followed by an explosive growth of more than 60% in newly approved trials in 2012. This could be explained by the notable increase in the number of "mandatory" registration trials in the sector for bioequivalence studies of generics made by both Russian and foreign companies (by a factor of three and nearly six times, respectively). However, the number of issued approvals for international multicenter clinical trials in 2012 remained at the 2011 level (370 vs.369), as reflected in Figure 1.[3]

Figure 1 also shows that the structure of the market also changed over the years following the introduction of the new law. By 2012, the market structure had shifted in the direction of trials on generic medicines, as the number of bioequivalence trials of generics conducted by both foreign and domestic sponsors increased.

FIGURE 1: Changes in the Number of Approvals for Clinical Trials Conduct, 2004-2013

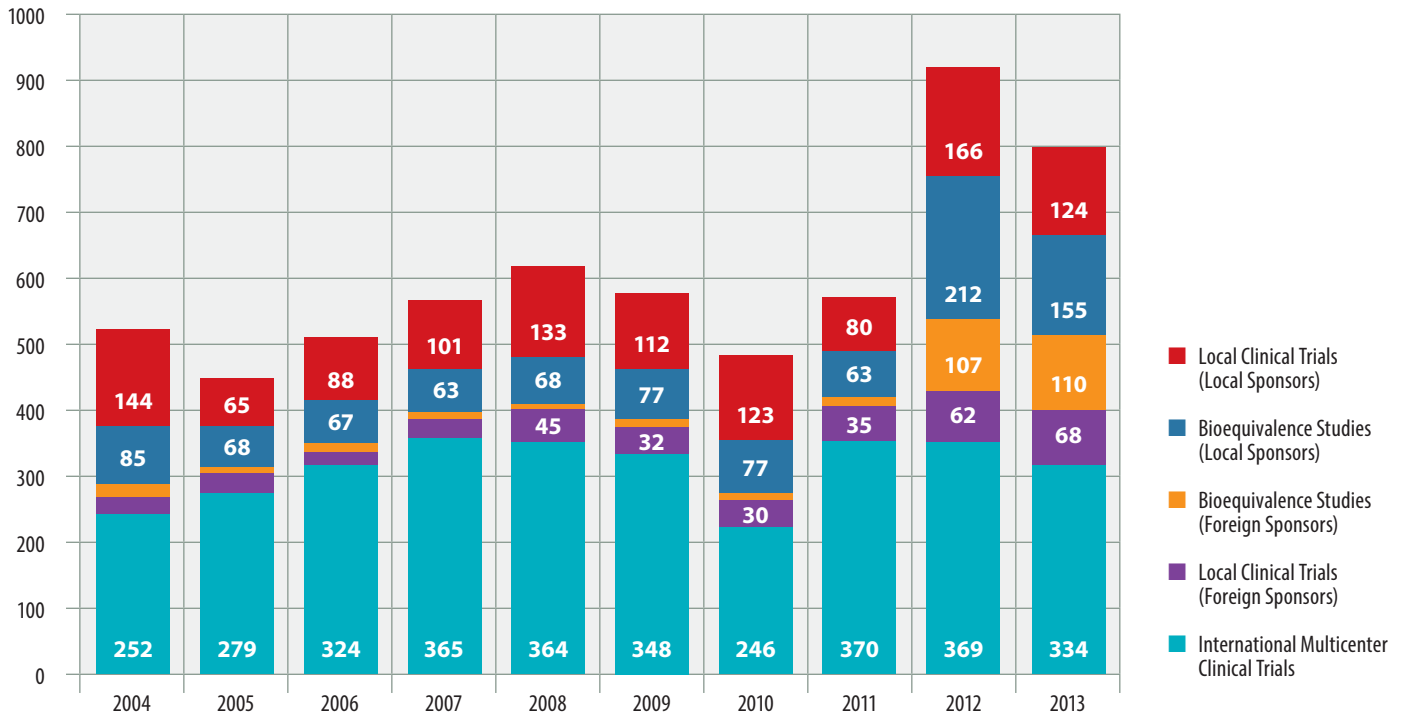
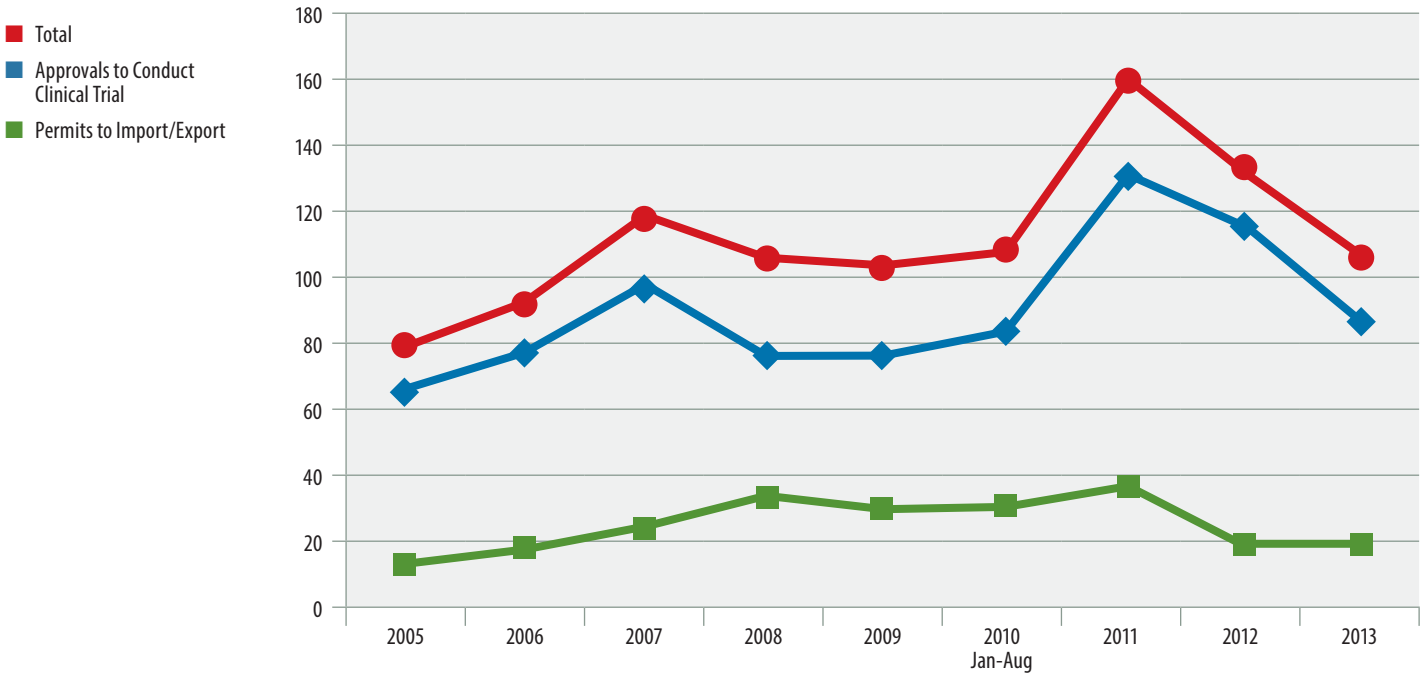


FIGURE 2: Changes in Average Timeframes in Days (2005-2013)



Statistics for Study Approvals

According to the new law, the process of receiving the initial study approval in the Russian Federation should be completed within 45 working days from the time of application. However, the official timelines do not account for the lengthy time intervals for document transfers from one department to another within the approving authority. There is a notable discrepancy between the amount of time permitted for completion of the process and the amount of time actually documented for the approval.

The dynamics of average approval times in recent years is shown Figure 2 (data collected by the Moscow-based Association of Clinical Trial Organizations since 2005).[3]

The worst statistics over the entire recorded time were in 2011, following the adoption of the law "On circulation of medicines" by the Ministry of Health and Social Development (MHSD), which was granted the study approval function. Similar to the processes required by any innovative regulation, the ministry had to go through restructuring and establish new procedures tied to the law. Restructuring in a context of limited resources made the adjustment period even more challenging.

Although the year 2012 showed significant improvement in comparison to 2011, the average time to obtain study approval was still higher than it was under "Roszdravnadzor" (the local Competent Authority, which issued the study approvals prior to the new law's implementation in 2010). The Ministry of Health showed better results than Roszdravnadzor in terms of the average times for issuing permits to import medicines and import/export biological samples.

The year 2013 showed results regarding import/export permits that were comparable to historical moving averages. For the second year in a row (2011, 2012) the metrics of the Russian Ministry of Health were better than those of Roszdravnadzor. The average times for obtaining study approvals and the total regulatory startup time through an approval process mediated by the Ministry of Health were also back to pre-reform levels and were almost on par with those recorded in 2009. Thus, in 2009 the average time to obtain a study approval was 77 days, and the total regulatory startup time was 107.5 days; in 2013, these numbers were 87 and 107, respectively.[3]

TABLE 1: Average Timeframes for Issuing Approvals, 2012 vs. 2013

Approval Type	2012	2013	2013 vs. 2012 (%)
To Conduct Clinical Trials	116	87	–25
To Import Medicines	18	14	–22.2
To Import/Export Biosamples	20	20	0
To Make Amendments to the Protocol	64	45	–29.7
Other Approvals (e.g., to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	41	26	–36.6

Table 1 demonstrates the average timeframes for obtaining certain types of approvals in 2012 and 2013,[3] indicating that the increased efficiency extended across studies with different objectives and designs.

Comparative Analysis of EU and Russian Legislation

In 2012 the European Commission and the Russian Ministry of Health collaborated on a project entitled "Cooperation in the Field of Clinical Trials."[4,5] A report on this project was prepared in September 2012, although it was only made accessible to the public in early 2013, after the document appeared on the European Commission website.

The report emphasized that most of the data from pivotal clinical trials submitted for marketing authorization applications to the European Medicines Agency (EMA) are from third countries, and that the Russian Federation is "one of the key players in this respect." In fact, the report noted that, "about 60 percent of all clinical trial data included in [Marketing Authorization] applications to the EMA has been generated outside the EU, and this underscored the importance of aligning foreign [Good Clinical Practice] systems," such as that of the Russian Federation with the EU.[4,5]

The report contains a detailed comparative analysis of EU and Russian legislation on clinical trials. It concluded that, "In general, it can be stated that for the conduct and supervision of clinical trials in the EU and the Russian Federation equivalence of the respective regulatory/legislative framework provisions is given."[4,5] This opinion allows the EU, and in particular the EMA, to accept the results of clinical trials conducted in Russian centers in accordance with the Russian legislation.

However, there are 17 legislative differences, classified by the report's authors into four categories:

- Country-specific requirements that go beyond those applied in the EU;
- Differences that might affect the trial participant's rights, safety, and welfare and the credibility of study data, and thus acceptance of the clinical study results by the EU drug regulatory authorities;
- Differences that restrict the nature and extent of trials that can be carried out in the Russian Federation, in a manner more restrictive than found in the EU; and
- Other, country-related, differences.

One of the most serious difficulties brought by the law is the requirement to conduct local "registration clinical trials." Regarding these, the report said: "In particular, the requirement to repeat safety and efficacy clinical trials (so-called local registration studies) whose results have already been assessed in the 'original' registration process, which put study participants on unnecessary risk(s), generate additional costs for the applicant, and postpone access of the population to modern medicines, should be re-assessed."

The authors of the report also criticized the standard under which clinical trials are included in the process of registration: "Except for so-called international multicenter clinical trials (IMCTs) and post-registration studies, applications for conducting a clinical trial in [the Russian Federation] can only be submitted in the course of a registration process."[4] The report recommends, "The link between [the] registration process and authorization to conduct a clinical trial should be removed." The intent of this modification is to disassociate the conduct of studies in Russia from the requirement that the interventional product be marketed in Russia.

Although there are no data suggesting that the new law has enhanced data integrity, its implementation has led to noteworthy changes in the clinical trials market in the Russian Federation in terms of interest in, approval of, and initiation of studies.

Among other elements in Russian legislation, characterized as "more strict" and "exceeding those in the EU," but not related to differences that could affect "the rights, safety, and welfare of trial participants, credibility of study data and thus acceptance of the clinical study results in the EU," the report's authors named problems that clearly slow development in the sphere of clinical trials in Russia and raise criticism from stakeholders. Identified differences between the relevant regulations in EU and the Russian Federation include[4]:

- "Direct contacts of an applicant with the Ethics Council or the Expert Organization are not allowed. This is different in the EU, where a dialogue between applicant[s] and drug regulatory authorities and Ethics Committees is considered to be beneficial."
- "Clinical sites for conducting clinical trials need to be accredited by the MHSD. Such an accreditation requirement is not reflected in the applicable EU regulations."
- "(Principal) investigators must have [five years of] experience in the conduct of clinical trials in order to be eligible as [an] investigator in a clinical trial. Such provision does not exist in the EU, but exists in the national legislation of member states like Germany, where [two years of] experience in the conduct of clinical trials is requested for investigators."
- "Clinical trials involving healthy volunteers (i.e., in Phase I studies) with 'medicinal products manufactured outside the [Russian Federation]' are prohibited, but for local sponsors are permitted. Also possible are Phase I studies with foreign drugs involving patients."

It was suggested that removing these key differences and other more minor points of departure named in the report would allow not only the harmonization of Russian legislation with European equivalents, but would also limit the excessive administrative barriers perceived for study conduct in the Russian Federation, enhancing the attractiveness of Russia for international trial programs. As of August 2014, these changes in regulations have yet to be implemented. Ongoing attempts to address at least some of these differences are being made by interested parties during discussions of the new law.

In general, the amendments to the existing statute aim to improve the procedures for state registration of medicines, address gaps in terminology, and provide guidelines on withdrawal of ineffective, unsafe, and substandard medicines from the Russian market.

An Impact Assessment

This review attempts to summarize the impact of the law "On circulation of medicines" and subsequent modifications, as indicated in the previously mentioned bill "On introducing the changes into the law 'On circulation of medicines.'" Taking into account the nature and frequency of criticism from both trialists as well as pharmaceutical sponsors, the work on amending the law "On circulation of medicines" started almost immediately after the law was introduced in 2010. Earlier versions of the bill carried sufficiently serious risks for the clinical trials market, given proposed requirements prior to study authorization.

For example, one early draft of the legislation planned to introduce a requirement for the pharmaceutical analysis of the samples of the study drug as a condition for obtaining a study approval. Although the intention of the requirement was understood, current state-of-the-art in good manufacturing processes obviated all potential benefit versus the encumbrance associated with compliance.

Another proposal by the Ministry of Health suggested increasing the time period for obtaining a study approval from 45 working days to 70 days. Fortunately, representatives from the pharmaceutical industry succeeded in convincing the lawmakers to abandon both of these ideas. As a result of long-term collaboration with the Ministry of Health, the pharmaceutical market participants and various other federal agencies managed to avoid a number of proposed requirements that, in effect, would do little to enhance data quality or subject protection.

Nevertheless, even the more refined version of the law retains substantive areas requiring revision. According to the Association of International Pharmaceutical Manufacturers (AIPM), "the review of the bill allows [one] to conclude that, despite the public discussion of the bill, most of the proposals of the professional community to harmonize regulatory standards with modern international standards, as well as to eliminate the serious shortcomings in the draft, have not been taken into account when developing current version of the Draft Law."[6]

What Will the New Bill Bring to the Drug Market?

In general, the amendments to the existing statute aim to improve the procedures for state registration of medicines, address gaps in terminology, and provide guidelines on withdrawal of ineffective, unsafe, and substandard medicines from the Russian market.

In the case of registration of orphan drugs, changes in the procedure for state registration will include the review of documentation on the individual drugs to determine if the indications meet the definition of orphan status in Russia. Additionally, there is no need to conduct local trials for this category of drugs as a part of registration in the Russian Federation (if the results of the international trials are available).

In the case of registration of generic (reproduced) drugs, the bill

a) lists the conditions under which it is no longer required to provide a report on the results of the therapeutic equivalence studies and

b) determines the conditions of the expedited review for state registration of such drugs.

Both modifications substantively increase the attractiveness of clinical investigations conducted in Russia for generic products.

In terms of the clinical research arena, the new bill seems to have either minimal effect or even some positive consequences, as it abandons the requirement for repeated local trials for orphan drugs and for redundant (and challenging) studies of efficacy and safety for nontablet forms of generic drugs. However, worthwhile attributes of the bill are counterbalanced by unresolved issues, such as mandatory accreditation of clinical sites as well as a requirement for five years of experience on the part of the principal investigator; both criteria are perceived as more stringent than those mandated within the EU. In addition, clinical trial insurance rules and conditions are still not harmonized with international practice, and ongoing issues with the conduct of pediatric studies have not been addressed.

Conclusion

Overall, the new bill "On introducing the changes into the law 'On circulation of medicines'" has prompted an active discussion within the pharmaceutical circles in Russia on the shape and details of oversight required for trial conduct. The dialogue itself has proven helpful, because of the diverse perspective of different stakeholders.

The new bill resulted in some subtle improvements of the current law "On circulation of medicines"; however, it still failed to address some of the major issues for the development of the biopharmaceutical market in Russia.

For example, AIPM has a critical view of the draft law specifically presented in its entirety: "Despite some certain positive aspects of the Draft Law concerning the regulation of orphan drugs and a number of administrative procedures in the registration of drugs in general, it appears that the bill does not solve the fundamental problems of the current circulation of medicines in the Russian Federation, ... but also to a large extent aggravates and multiplies them."[6] The collaborative efforts of many different individuals representing diverse stakeholders will likely be required to assure that improvement in the law regulating clinical trials in the Russian Federation will continue.

Acknowledgments

The authors would like to acknowledge Svetlana Zavidova, executive director of the Association of Clinical Trials Organizations (ACTO), for sharing a comprehensive view on the status of the pharmaceutical market in Russia and permission to use ACTO documents. The authors also wish to acknowledge the editorial review of Michael F. Murphy, MD, PhD, chief medical and scientific officer for Worldwide Clinical Trials.

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The collaborative efforts of many different individuals representing diverse stakeholders will likely be required to assure that improvement in the law regulating clinical trials in the Russian Federation will continue.

OPEN BOOK TEST

This test expires on December 31, 2015

(original release date: 12/01/2014)

Is the GUDID a GOOD IDea? Can Unique Device Identification (UDI) and Global UDI Database (GUDID) Improve Medical Device Development and Surveillance?

1. **Clinical studies for premarket devices are designed to do which of the following?**

1. Gather scientific data
2. Support safety claims
3. Gather pricing information
4. Support efficacy claims

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

2. **Medical Device Reports (MDRs) must be submitted to the U.S. Food and Drug Administration (FDA) in an electronic format so that the FDA can do which of the following with them?**

1. Review
2. Process
3. Archive
4. Distribute

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

3. **Whom does the FDA encourage to submit voluntary reports?**

A. Importers
B. Manufacturers
C. Couriers
D. Caregivers

4. **To which company did the FDA grant a contract for the Pharmacovigilance Report Intake and Managed Output (PRIMO) software to replace the MAUDE system?**

A. September Funding Group
B. October Flying Group
C. November Research Group
D. December De-Icing Group

5. **How many MDRs of suspected device-associated deaths, serious injuries, and malfunctions does the FDA receive each year?**

A. Several hundred
B. Several thousand
C. Several hundred thousand
D. Several hundred million

6. **MDRs currently submitted to the FDA raise which of the following concerns?**

1. MDR data do not make it possible to compare event rates between devices.
2. MDR data cannot be used to monitor device performance.
3. MDRs cannot detect potential device-related safety issues.
4. MDR data alone do not allow evaluation of a change in event rates over time.

A. 1 and 2 only
B. 1 and 4 only
C. 2 and 3 only
D. 3 and 4 only

7. **After full implementation, the Unique Device Identification (UDI) system can do which of the following?**

A. Allow more accurate reporting
B. Complicate the review
C. Eliminate analysis of reports
D. Increase medical errors

8. **The UDI system has the potential to help the FDA in which of the following ways?**

1. To identify product problems more quickly
2. To archive reports automatically
3. To target recalls better
4. To improve patient safety

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

9. **The UDI final rule is expected to substantially reduce existing obstacles to the identification of devices used in which of the following regions?**

A. Asia-Pacific
B. Europe
C. United Kingdom
D. United States

10. **What conclusion can be drawn about the FDA's requirements for UDI?**

A. They will lead to improvements in several areas.
B. They will highlight information about frequency of device use.
C. They might increase speed to market.
D. They will not balance pre- and postmarket data.

Clinical Research in India

11. **With reference to clinical research in India, this article explores which of the following?**

1. Reasons for conducting clinical research in the Indian market
2. The issues that have occurred
3. Response of the global clinical research community
4. Regulatory reactions that have resulted

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

12. **Which of the following are the greatest resources for conducting clinical trials in India?**

1. Huge patient population that is genetically diverse
2. Large talent pool to conduct all aspects of preclinical and clinical research
3. Significantly lower trial cost compared to trials conducted in the U.S.
4. Informed and highly educated test subjects

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

13. **What were the negative consequences of the rapid onset of clinical trials in India?**

A. Government kickbacks resulting in compromised studies and harm to patients
B. Accusations of unethical behavior among study investigators and study sponsors
C. Ban of clinical trials in India by the global community
D. An exodus of Indian researchers and talent pool from India to other countries

14. **Examples of unethical behaviors by study investigators and study sponsors include which of the following?**

1. Poor informed consent procedures
2. Little or no compensation for injuries
3. Abuse of authority to enroll subjects in clinical trials
4. Manipulating data to show positive results

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

15. **What action did the Indian Supreme Court take in response to the need to reform the way clinical trials are conducted?**

A. Appointed a clinical trials czar and assigned a government official for each clinical trial
B. Declared the results of all clinical trials in question as invalid and levied huge fines on the researchers
C. Banned the opening of studies across the country until adequate resolutions were in place
D. Required stringent academic regulation for personnel involved in each stage of the trial

Find the most current online test at **www.acrpnet.org/homestudy**, including any revisions made after publication of this issue of *Clinical Researcher*.

16. **The reform for making clinical trials more transparent places emphasis on which of the following?**

1. Monetary compensation for all patients
2. Change in the consent process
3. Medical management
4. Financial compensation for a clinical trial–related injury

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

17. **Medical management and compensation of patients in clinical trials strives to achieve which of the following?**

A. Streamline the process of conducting a clinical trial
B. Allow investigative reporting by media
C. Make the conduct of fiscally responsible trials possible
D. Place patient care first during the clinical trial

18. **What is the purpose of the Clinical Trials Registry of India?**

1. Provide public information on clinical trials
2. Inhibit compliance violations and the nonreporting of negative trial results
3. Report only published studies in India
4. Follow direction from the clinical trials czar

A. 1 and 2 only **C.** 2 and 4 only
B. 1 and 3 only **D.** 3 and 4 only

19. **Based on clinical professional opinions on ethics in clinical trials in India, what are the top three concerns?**

1. Informed consent process
2. Financial compensation for study site
3. Empowerment of the ethics committee
4. Patient awareness of safety

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

20. **The survey results of the clinical research professionals' opinions on ethics in India indicated which of the following?**

1. The study investigators pay increased attention during the study and provide speedy trial results.
2. The need to record is explained and alternatives to trial participation are presented during the informed consent process.
3. An adequate informed consent process does not exist and ethics committees do not operate independently.
4. There is decreased oversight by the principal investigator and falsification of trial results is common.

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 3 and 4 only

The "On Circulation of Medicines" Law in Russia: Four Years Later

21. **Reflecting changes over the years since the new law "On circulation of medicines" went into effect, by 2012 the Russian market structure had shifted toward which of the following types of trials?**

A. Orphan drugs
B. Post-registration
C. International multicenter
D. Generic medicines

22. **What is the official timeline for obtaining study approval in Russia?**

A. 45 working days **C.** 107 working days
B. 77 working days **D.** 180 working days

23. **Most of the data from pivotal clinical trials submitted for marketing authorization applications to the European Medicines Agency (EMA) are from Third-World countries (including Russia). What percentage of all clinical trial data included in marketing authorization applications to the EMA is generated outside the European Union (EU)?**

A. 50% **C.** 70%
B. 60% **D.** 40%

24. **The analytical report on Cooperation in the Field of Clinical Trials identified four categories of legislative differences between the EU and the Russian Federation, including which of the following?**

1. Country-specific requirements that go beyond those applied in the EU
2. Differences that might affect the trial participant's rights, safety, and welfare; the credibility of study data; and thus acceptance of the clinical study results
3. Country-specific requirements that go beyond those applied in the Russian Federation
4. Differences that restrict the nature and extent of trials that can be carried out in Russia in a manner more restrictive than those in EU

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

25. **According to the existing federal law "On circulation of medicines," what is the minimum clinical trials experience that a principal investigator in Russia is required to have?**

A. One year **C.** Five years
B. Three years **D.** Ten years

26. **As a result of criticism from and discussion with pharmaceutical industry representatives, lawmakers had to abandon which of the following ideas for amendments to the new law?**

1. Requirement for the pharmaceutical analysis of samples of the study drug as a condition for obtaining study approval
2. Suggestion to increase the time period for obtaining study approval from 45 working days to 70 days
3. Suggestion to increase the time period for obtaining study approval from 45 working days to 120 days
4. Inclusion of additional documents in the clinical trial application package

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 3 and 4 only

27. **Which of the following are the general aims of the new bill "On introducing changes into the law 'On circulation of medicines'"?**

1. To improve the procedures for state registration of medicines
2. To make the clinical trials expertise of applicants more transparent
3. To address the gaps in terminology
4. To provide guidelines on withdrawal of ineffective, unsafe, and substandard medicines from the Russian market

A. 1, 2, and 3 only **C.** 1, 3, and 4 only
B. 1, 2, and 4 only **D.** 2, 3, and 4 only

28. **In accordance with the new law, which of the following are the changes in the procedure for registration of orphan drugs?**

1. Review of documentation to ensure drug indications meet the definition of orphan drug status in Russia
2. Waiver of the requirement to conduct local clinical trials if the results of international studies are available
3. Need for the drug indications to meet the definition of orphan status worldwide
4. Requirement to conduct both the local clinical trials and international studies

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 3 and 4 only

29. **Which of the following characteristics of the new bill potentially increase the attractiveness of clinical studies for generic products in the Russian Federation?**

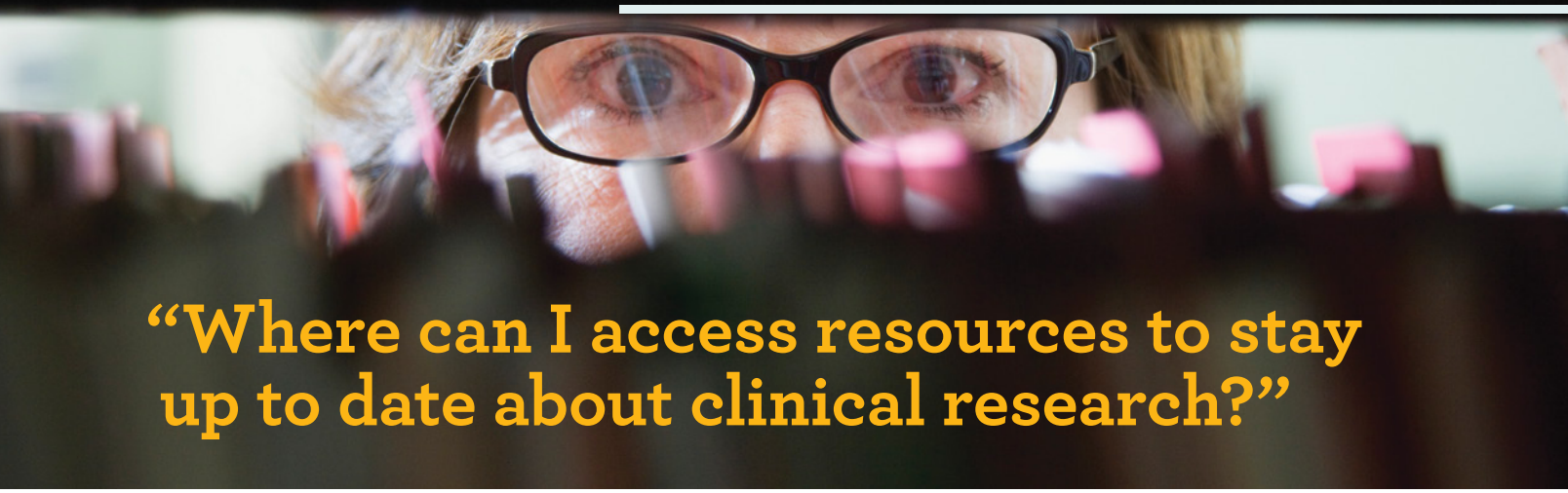
1. It determines the conditions of the expedited review for state registration of generic drugs.
2. It states that the results of international bioequivalence studies are sufficient for registration in Russia.
3. It states that the results of international bioequivalence studies are mandatory for registration in Russia.
4. It lists the conditions under which it is no longer required to provide a report of therapeutic equivalence studies.

A. 1 and 2 only **C.** 2 and 3 only
B. 1 and 4 only **D.** 3 and 4 only

30. **The new bill "On introducing changes into the law 'On circulation of medicines'" seems to have minimal effect on which of the following elements of the drug development and approval process?**

A. Basic science research
B. Manufacturing
C. Sales and marketing
D. Clinical trials

Mary White, MS, MSHI, AHIP, EMT-B



"Where can I access resources to stay up to date about clinical research?"

In considering the theme of this issue, we column editors thought, "We're really lucky to work at an academic medical center and have so many resources available if we have questions about any local or global regulatory questions a coordinator may face." After realizing that everyone may not be lucky enough to have so many easily accessible resources, we asked one of our best resources, the knowledge management librarian at the North Carolina TraCS Institute, if she would be willing to compile a list of some reputable resources that are available to all. We are pleased to present Mary White as special guest columnist for this issue.—*CRC Column Editors Claudia G. Christy, RN, MSN, CCRC, and Laura B. Cowan, MA*

Clinical research professionals have a wide variety of information needs to help them accomplish their daily work. This may include looking for the latest information on grant and program development; help with enrollment, supervision and education of participants; collection and management of data; and knowledge about compliance with regulations and policies.[1,2]

One survey of clinical research professionals indicated that, although nine out of 10 search the biomedical literature at least once a month to support their work, just under half felt limited in their confidence to locate the information they needed.[1] In addition, some may not physically have the information, books, or articles they need at hand.

Because time and financial resources are often limited, here are three strategies and tools to help you:

1. Determine what information you need to support your work,
2. Get access to that information, and
3. Find people to help support this process.

Although many academic and medical institutions purchase subscriptions and access to specific websites, databases, journals, and books, this column focuses on those that are freely available to all.

Determine What Information You Need

How and where do you keep up with the most recent changes in science and policy, to ensure the integrity of your research protocol and protect the safety of your research participants?

Search Through Journals and Books

Late-breaking ideas and grounded research knowledge are available in the biomedical literature. You may need to access this information when doing preparation work for grant proposals or program development. Thousands of journals and books exist. Fortunately, databases, catalogs, and indexes can help you quickly find the information you need, just by searching for topics or subjects you want to find more about.

If you have any favorite resources for industry trends or emerging health information, please send them to **crcperspective@unc.edu**

PubMed (MEDLINE)[3] is the biomedical database produced by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine. It includes more than 21 million citations to items found in health and life sciences journals and books.[4] In some cases, where free articles exist, PubMed directly links to the article.

For those internationally focused or located, the World Health Organization's (WHO's) **Global Health Library**[5] provides expanded access to scientific evidence and health information from across the WHO regions and libraries.[4]

Scan Synthesized Sources of Information

Although searching through the literature gives you direct access to articles, sometimes it helps to read a synthesized version by topic. The following websites do just that.

Sometimes referred to as the free UpToDate, **Medscape**[6] offers background topic reviews on many diseases and treatments, as well as subject specialty sites including one for clinical trials. Access is through free registration, and the site contains numerous advertisements.[4]

Prepared by the Centers for Disease Control and Prevention, the **Morbidity and Mortality Weekly Report**[7] provides timely, reliable, authoritative, accurate, objective, and useful public health information and recommendations, discussing disease trends and issues.

The U.S. Government also provides several websites with information useful for those running clinical trials. Created by the National Library of Medicine within the National Institutes of Health (NIH), **ClinicalTrials.gov**[8] is the world's largest clinical trials database. It is the registry for researchers to enter and download information about publicly and privately supported trials, as well as a resource for the general public to learn more about existing clinical trials. More information about reporting mandates is available on the website.

The U.S. **Food and Drug Administration (FDA)** also offers a "Clinical Trials and Human Subject Protection"[9] web portal, with information about regulatory compliance, "Good Clinical Practice," and guidance documents. In addition, the U.S. Department of Health and Human Services' **Office of Research Integrity**[10] and the **Office for Human Research Protections (OHRP)**[11] offer excellent resources about ethical research conduct, including interactive simulations and videos about research misconduct, such as "The Lab"[12] and "The Research Clinic."[13]

A more global view of some regulatory issues for those working with pharmaceuticals is available from the **International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use**.[14] The OHRP also offers the 2014 edition of the **International Compilation of Human Research Standards**,[15] which includes such issues as informed consent, reporting requirements, and other guidelines on human subject protection in more than 100 countries.

Share Information with Your Research Participants

In one study of coordinators, when asked to identify the key features of their work duties, many respondents immediately spoke of their interactions with others, namely the clinical research participants.[2]

Part of the clinical researcher's role may be to educate the research participant about health conditions related to the study. More and more, people are turning to the Internet for health information, which is one of the top uses of the Internet. In order to surf the web in a "healthy" way, consumers should consider a variety of issues, including the website's source, quality/evidence, currency, potential bias, and protection of the consumer's privacy.[16] Clinical research professionals can help guide research participants in this endeavor, pointing them to quality sources of health information.

MedlinePlus[17] is a "one-stop shop" of information to help answer research participants' health questions. It brings together authoritative information from governmental, nonprofit, and other health-related organizations. The website includes a variety of resources including the A.D.A.M. medical encyclopedia, drug information, healthcheck tools, more than 165 interactive health tutorials, and information in easy-to-read language as well as languages other than English.[4]

Get Access to the Information You Want from Books and Journals

Although many academic and medical institutions pay for biomedical journals and books, many publications don't require payment to read them. Here's how you can find some of them.

PubMed Central (PMC)[18] was created by the NCBI as a free full-text digital archive of biomedical and life sciences journals.[4] Pursuant to the NIH Open Access Policy, the final version of all articles

How and where do you keep up with the most recent changes in science and policy, to ensure the integrity of your research protocol and protect the safety of your research participants?

resulting from federally funded research are submitted to PMC, where you will find more than three million articles.

Some scholarly journals freely available through "open access" related to clinical research include: *Open Access Journal of Clinical Trials,*[19] *Journal of Clinical Research Best Practices,*[20] and the *Journal of Clinical Research and Bioethics.*[21] **See the Directory of Open Access Journals**[22] and **BioMed Central**[23] for more open access journals.

Although numerous texts exist, there are a few **free reference books focusing on clinical research,** such as the *Good Clinical Practice Resources Guide* (NIH Division of Microbiology and Infectious Disease)[24] and the *Handbook for Good Clinical Research Practice: Guidance for Implementation* (WHO).[25]

If you don't have a journal or a book that you need, remember three letters: I-L-L! Ask at your home library about an **interlibrary loan** to borrow the material. The books and journals you want may be free or available at a small cost.

Get Help from Others

Ask A Librarian! When you don't have time or are having trouble finding answers to your questions, consider contacting a librarian, a professional trained to help you efficiently navigate these resources and more. Librarians can search the literature for you, make suggestions as to where you can find information to address your question, as well as find specific books and journals.[1]

Even if you don't have a librarian at your place of work, you can freely contact librarians who all have a mandate to serve the public at publicly supported state research universities, medical centers, community colleges, and community libraries. Many libraries provide support virtually, where you can ask your questions through phone, e-mail, and chat.[4]

Keep in Touch with Your Colleagues. The Association of Clinical Research Professionals[26] provides many resources to its members, including an online community, local chapters, and annual conferences. Also, reaching out to other clinical research professionals through networking tools such as LinkedIn gives you support regardless of your current affiliation.

In summary, even though you may be one coordinator in a small rural practice, many resources are available to you for little to no charge. Keeping up to date to provide reputable information to your participants and staff is easier than ever if you know where to look. We hope that these resources will be helpful to you.

What are your thoughts?

Do you have any favorite resources for industry trends or emerging health information? Share your tips for staying up to date, and look for more ideas in future columns.

Acknowledgments

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DOES DESPERATION JUSTIFY DEPARTURES FROM ETHICAL STANDARDS?

The Case of the Ebola Epidemic

PEER REVIEWED OPINION | Philip M. Rosoff, MD, MA

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In 2007, I was a member of a taskforce empanelled by the North Carolina Institute of Medicine and charged with creating a proposal to ethically confront what was expected to be a major, worldwide pandemic of influenza. It was feared that it could create havoc, panic, and deaths that might equal, if not exceed, those experienced in the great pandemic of 1918–19. Any number of nightmare scenarios were proposed and considered, ranging from mild disruptions to schools and public services to overwhelming breakdowns of public order. Indeed, many of the smaller, localized events that have accompanied the spreading Ebola epidemic in Sierra Leone, Liberia, and Guinea (and to a lesser extent, Africa's most populous country, Nigeria), such as riots and looting, were all anticipated as possible should influenza rapidly spread and incapacitate the fragile public health structure of the United States.

The scope and complexity of many of the healthcare delivery issues covered by the influenza taskforce are too deep to consider here; I would refer interested readers to other sources.[1–6] However, we did discuss how to confront the demand for existing medications that undoubtedly would rapidly become scarce, so the central theme here was fair allocation.

Another major area we examined was how to meet the anticipated shortage in healthcare providers whose numbers would be inadequate to meet demand, both because of the large number of patients and the possibility of widespread outages due to worker influenza. Would any doctor, we asked, no matter how little skilled or knowledgeable in the care of very sick patients, be better than no doctor at all?

Could a massive healthcare crisis of this sort permit the otherwise impermissible?

Unfortunately, we were unsuccessful in developing satisfactory guidelines to regulate possibly dangerous practice, even when performed with the most altruistic of intentions. The question remained, could a massive healthcare crisis of this sort permit the otherwise impermissible? If so, should there be any restrictions, controls, regulations, or caveats, or are good intentions sufficient to justify what might otherwise be viewed as negligent actions? Not surprisingly, the current Ebola epidemic has again raised these questions, and people are providing answers borne of their desire to do something—anything—to help.

Ebola presents challenges similar to pandemic flu, but also unique. Although some resources may be in short supply to meet the demand, the world's response to the epidemic will likely lead eventually to minimal shortfalls of the most essential provisions, medicines, and facilities. Thus, the most difficult questions associated with prioritization and scarce resource allocation will not have to be faced.

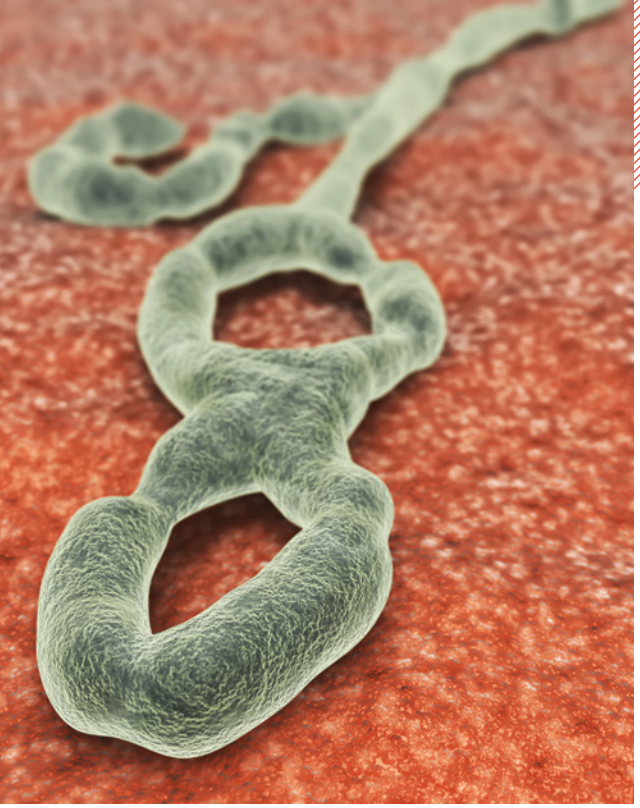
The second major area centers on considerations of whether standards of care—be they local, regional, or universal—are inviolate or may be altered to meet the demands of a crisis. The latter almost always involves lowering benchmarks of excellence or requirements of quality due to the desperation of the situation, assuming somewhat simplistically that it is better to do something rather than nothing. If this view is adopted, what conditions would warrant such actions, and how much of a departure from standard operating procedure would be too much?

BACKGROUND

At the time of this writing, there have been almost 10,000 cases of Ebola reported, with a mortality rate of 75%, consistent with previous outbreaks in West Africa.[7] Ebola is a filovirus—so-called because of its filamentous shape observed on electron micrographs. There are at least five species, of which two seem to be responsible for most of the major epidemics to date.[8] All have been self-limited and regionally localized. The virus is most likely endemically harbored in bats (and possibly rats), and may cross over into the human population by ingestion of infected animals consumed for food. It is unclear what factors trigger outbreaks, although it may be due to host features such as concomitant infection.

Once resident in humans, Ebola is easily transmissible by contact with body fluids and is highly virulent. There is an asymptomatic incubation period of days to a couple of weeks. Patients then present with nonspecific symptoms of viral infections such as fever, malaise, and myalgias, which can then progress rapidly to multi-organ failure and a systemic coagulopathy. The clinical picture resembles overwhelming sepsis.

There is no specific anti-infective treatment or preventive vaccine available (more on this later), thus the approach to management is symptomatic. Ideally, this would include advanced intensive care as indicated. Not surprisingly, these kinds of labor and resource-demanding facilities, personnel, and materiel are in limited supply in the locales most affected by the current epidemic.[9,10] It may be that the lack of public health, advanced medical care, and other resources contributes to the high fatality rate and that more modern, extensive, and expansive hospitals and infrastructure, such as found in most developed nations, could lead to a much improved prognosis. There is little evidence, however, to support this conjecture.



Ebola is a filovirus—so-called because of its filamentous shape observed on electron micrographs. There are at least five species, of which two seem to be responsible for most of the major epidemics to date.

The most effective way to prevent transmission and further dissemination is by standard, relatively straightforward public health approaches such as isolation, contact tracing, and quarantine, none of which requires sophisticated medical infrastructure. They do, however, demand a level of on-the-ground intervention and coordination that has not so far been achieved in order to keep up with the virus. Although there is a fear that Ebola could spread beyond the three countries most affected and move to Europe and the Western Hemisphere, Dr. Anthony Fauci, the director of the U.S. National Institute of Allergy and Infectious Diseases of the National Institutes of Health, has written:[8]

> Although the regional threat of Ebola in West Africa looms large, the chance that the virus will establish a foothold in the United States or another high-resource country remains extremely small. Although global air transit could, and most likely will, allow an infected, asymptomatic person to board a plane and unknowingly carry Ebola virus to a higher income country, containment should be readily achievable. Hospitals in such countries generally have excellent capacity to isolate persons with suspected cases and to care for them safely should they become ill. Public health authorities have the resources and training necessary to trace and monitor contacts. Protocols exist for the appropriate handling of corpses and disposal of biohazardous materials. In addition, characteristics of the virus itself limit its spread.

This statement emphasizes that appropriate and well-tested public health measures can contain and control the Ebola epidemic, notwithstanding the lack of effective antiviral treatments. As I write, there have been four cases brought to the U.S. for treatment, one true imported case from Liberia, and two confirmed infections of healthcare workers already in the U.S. by the latter case.

Nevertheless, the fear continues that Ebola could easily spread to Europe, the U.S., and Asia due to easy accessibility by air and sea, and thereby convert what has been a geographically confined epidemic to one that is widespread, if not global.[11] Certainly, the media has devoted time to this topic far exceeding its actual risk of occurring, thus stoking the concern. By the same token, the United Nations has declared the current outbreak a threat to world security, which in light of its current progression, does not appear to be public relations hyperbole.[12] It certainly could be a major danger to West Africa, especially if it is successful in spreading to Nigeria, as the Centers for Disease Control and Prevention's latest worst-case projections suggest.[13]

In the absence of effective medical countermeasures other than quarantine, isolation, and intensive supportive care, what else can be done? Does the current crisis warrant loosening accepted and understood standards of care in a desperate attempt to stem the developing disaster? There is a thin, but often ill-determined, border separating emergency situations from those breeding desperation, which itself can create further fear and even hysteria. Measures taken to combat the former, which can seem reasonable, may all too readily transform to less considered responses stimulated by desperation and hopelessness.

DESPERATION

In the "battle" against serious and potentially fatal diseases, doctors and nurses caring for patients often adopt warlike metaphors, and are willing—and can easily persuade their patients and their families—to accept increasingly risky and toxic therapies in an attempt to extend life, sometimes at tremendous costs. Many view these audacious physicians as intrepid warriors ready to employ imaginative and creative means in bold strikes against an indomitable foe for which there are few, if any, proven and effective means of treatment.[14]

It is often claimed that the desperation of patients and the grimness of their situations merit taking any chances that may offer themselves to give hope where none may actually exist. A cooler and more considered analysis could suggest that hope might not be worth the price to the individual patient and the potential damage to the social order of medicine engendered by a reckless use of interventions stimulated by terrible circumstances. Desperate situations may thus breed unwise, even dumb and counterproductive or destructive, solutions.

DESPERATE SOLUTIONS

One of the most commonly suggested desperate solutions, both in "regular" practice (as described above) or in situations where accepted and presumably proven effective therapeutic approaches are lacking, is to employ methods that abandon the normal standards of care or research by which we regulate the practice of medicine and human subjects investigation to monitor the tension between benefit and risk. For example, one could use previously untested medications or procedures (i.e., "first in humans") that have presumably demonstrated some therapeutic activity either *in vitro* and/or *in vivo* in experimental animal surrogate systems.

Another method might attempt to "repurpose" previously approved medications, such as those endorsed by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) for specific clinical indications as "safe and effective," and for which there may be theoretical scientific reasons to believe they might have efficacy in the new clinical situation.[15] This activity forms the basis for much "off-label" use in the U.S. and elsewhere.[16]

Further, drugs that are currently under investigation, but have not yet been approved, could be hurried along or taken off this regulatory path and used perhaps precipitously (in the U.S., this may be illegal[17]). This strategy was adopted at the height of the HIV pandemic in the U.S. under pressure from AIDS patient advocacy groups.[18,19] However, there are definite drawbacks to this approach, as noted by Eichler.[20]

All of these tactics must be viewed through the lens of being employed in third world countries, whose populations have a long and sordid history of being victimized and exploited in clinical research performed by developed world pharmaceutical companies. I will consider each one of these methods in turn.

It should be mentioned at this juncture that a hastily assembled panel of experts brought together by the World Health Organization (WHO) endorsed the use of unproven investigational drugs under appropriate ethical guidelines, including transparency, fair access, and allocation, and turning the information obtained from their use to the benefit others.[21] As will be discussed below, these recommendations are both anodyne and meaningless in this context.

WHICH WAY TO GO?

The world of drug development is in large measure a crapshoot. Even with the advent of advanced molecular modeling, supercomputer targeted drug design, and the like, the percentage of pharmaceuticals that enter the development pipeline and then emerge as fully formed medications that can be judged both safe and effective is vanishingly small. Indeed, the rate of approvals for new drugs has not improved much over the last 20 years or so.[22,23]

> In the absence of effective medical countermeasures other than quarantine, isolation, and intensive supportive care, what else can be done? Does the current crisis warrant loosening accepted and understood standards of care in a desperate attempt to stem the developing disaster?

Thus, our ability to predict therapeutic efficacy in combination with an acceptable margin of safety in *humans* is remarkably shaky. Not only is success of forecasting based upon chemical and biological data relatively poor, but proficiency at translating animal data to humans rests on a similarly unsteady foundation. Hence, using preclinical data to predict therapeutic activity in patients is a precarious enterprise that should be approached with caution.

Although the published information to date suggests that a variety of drugs, ranging from humanized monoclonal antibody cocktails such as ZMapp® to small interference RNAs ("iRNA") to novel antivirals, are effective against Ebola or a similar virus in nonhuman primates, it is difficult to know what might happen (including unexpected toxicities) when these drugs are administered to people.[24–26] Moreover, the supplies of these medications are so small that, if the decision were made to go forward with using them in patients, one would then be faced with the challenge of deciding who amongst the thousands of potentially eligible patients should receive the few doses available.

Administering investigational agents in such a scattershot random (but not randomized) manner would eliminate any opportunity to learn whether they were effective (or safe). If a recipient got better, one would truly not know if he or she would have gotten better anyway. Conversely, if the recipient did not get better, one would never be able to tell if the drug was ineffective or if the patient simply failed to respond. In addition, if there was suspected toxicity, the ability to ascribe it to the drug would be highly questionable.

Finally, the risks of exposing patients to the unknowable would themselves be unknowable and therefore unacceptable, especially in those who are desperate and would therefore cling to any hope held out to them, no matter how unrealistic or even dangerous. In sum, nothing could be learned from this experience. No one in the future could benefit, and we would never be able to recognize if anyone in the present did either.

Similar problems present themselves with "repurposing" current drugs, mostly without the unknown toxicity part, although one would not be able to know whether there would be unanticipated negative interactions with Ebola infection itself; indeed, this might not be unexpected with patients this sick. In any event, using drugs off-label in this manner might seem to introduce fewer problems,

The risks of exposing patients to the unknowable would themselves be unknowable and therefore unacceptable, especially in those who are desperate and would therefore cling to any hope held out to them, no matter how unrealistic or even dangerous.

but one is still left with the inability to draw any conclusions unless one used these medications within the confines and strictures of a controlled, randomized clinical trial.

In the case of Ebola, since there is no existing effective treatment beyond supportive care, the control arm would have to be a placebo. It is distinctly possible that neither physicians nor patients would find such conditions acceptable, given that these drugs would be commercially available and thus could be readily obtained without having to enroll in the trial. Moreover, randomization of subjects is a difficult enough concept for people to accept under normal circumstances; adding the stress of life-threatening illness might make it intolerable.

Last, fast-tracking of investigational drugs that have entered the clinical trial pipeline but for which little information on safety or efficacy is available may be feasible, but it entertains many risks similar to the two other approaches. The only difference is that the study of the drug(s) in humans would be a bit more developed, even though the hypotheses upon which they are being investigated may be comparably incorrect. Many drugs fail to make it to approval at all the stages of development, not simply at the beginning, and it is almost impossible to predict where the problems will appear. Finally, the history of fast-tracking in the U.S., especially with promising anticancer drugs, has not borne out the hope of providing more medications more quickly; the limited success rate has remained virtually unchanged.

One significant difficulty that afflicts investigational drugs is the fact that they are usually available only in relatively small quantities. No responsible drug company is going to invest large sums of money producing vast amounts of a drug for which the odds would predict a hasty demise. Thus, the world's supply of ZMapp® was limited to an amount sufficient to treat just a few people. The decision was made (it is unclear by whom) to administer it to two American healthcare workers operating in one of the afflicted countries, and to a Spanish priest. The Americans recovered, and the Spaniard died.

Under ordinary circumstances, one could conclude either that this favored already privileged Westerners over their impoverished patients or that it was believed that it was better to not expose Africans to the unknown risks of the drug and hence exploit their desperation. Either way, we will never know if the drug was effective or if Ebola or the drug killed the Spanish priest because of the way in which the affair was conducted.

Of course, one could potentially justify treating healthcare workers first (if one had access to an effective drug) as a form of reciprocity for their willingness to undergo the risks of constant exposure to infected patients. However, this would have to be made explicitly clear to all concerned in an attempt to earn their acquiescence, if not active endorsement, to be ethically sound. In the preparedness plans for pandemic influenza, priority for vaccine supplies was given to frontline healthcare workers, but the rationale was based on keeping them healthy to care for the ill, and not on "paying" them for their risky jobs. Most plans decided that doctors and nurses who got very sick with the flu would not be advantaged over anyone else in a similar clinical situation.[27–32]

SUMMARY

As horrible as the Ebola calamity is, it is taking place in an area in which there exist multiple endemic causes of premature death, including malaria, numerous diarrheal diseases, tuberculosis, HIV, and chronic malnutrition, to name but a few. Though not discounting the tragedy of Ebola, the few thousand to half a million deaths that could result before the outbreak is checked pale in comparison to the annual toll resulting from the regular mortal threats that occur as constant background dangers to the people who live in the region.

The key to confronting and controlling Ebola lies not in yielding to emotion wrought by desperation and engaging in ethically questionable practices using drugs that have yet to be tested fully in humans. Rather, the time-honored practices of public health measures such as quarantine, contact tracing, and the like, which we know are effective in infectious outbreaks and have previously worked with Ebola, should be the first line of offense.[33]

When and if medicines and/or vaccines become available, they should be studied to determine their safety and efficacy, as we would any other investigational drug. We can thus learn which to keep and which to discard as ineffective or too toxic (or both). Furthermore, they should be studied in the population most affected by the epidemic. The companies making the agents should pledge (perhaps with the financial and regulatory assistance of the WHO, wealthy Western governments, the FDA, the EMA, etc.) to make good treatments readily available and affordable to patients. Picayune squabbles over patents and profits should not prevent access by those most able to benefit, but perhaps least able to afford expensive first-world medicines.

Finally, once effective interventions are discovered, it will take some time to ramp up production of a virtually unlimited supply. This inescapable feature of manufacturing should neither warrant shortcuts to enhance supply (such as releasing drugs before they have been properly tested for

Links to major media coverage of the Ebola outbreak are being updated regularly at www.acrpnet.org/MainMenuCategory/Resources/News/ACRP-Wire/InTheNews.aspx.

sterility and stability), nor holding on to existing stocks until there are sufficient amounts for all. Thus, there must also be an ethically justifiable rationing allocation plan for the first, limited supplies. Now is the best time to create such a plan, in anticipation of future success, and there are numerous published methods for how to do this.[4,5]

I fully realize that the strictures that I have outlined here seem counter to our deeply felt intuitions and desires to do something, anything, in the face of the suffering of this epidemic. However, compassion and adherence to these ethical guidelines are not mutually exclusive. As terrible as this current Ebola outbreak is, it is not the end of the world. Many more appalling threats to health and prosperity endemic in this part of the world also deserve our empathy and compassion, but this fact does not license ignoring the current crisis. Nor does it sanction abandoning endorsed ethical standards simply because of desperate circumstances.

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Jeff Kingsley, DO, MBA, MS, CPI, FAAFP

Global Regulatory Insights: Why Do We Have Regulatory Compliance Professionals?

A natural follow-up to the query presented in the title for this column is, "What's the difference between law, regulation, and guidance?" We seldom really think of these things, but it's important to understand them.

Finding that tiny area of overlap where we're in compliance with all the laws, regulations, and guidance such that we can successfully conduct research, improve healthcare, and transact business can be tough. Sometimes, it's impossible.

I would argue that the difference is the amount of gray, as opposed to black and white. If the world were black and white, we would only have absolute law; there would be no need for regulatory compliance professionals. Of course, I know a few regulatory compliance professionals who would argue that the world is black and white, and that their job is to help show me that the gray world I see before me is a symptom of my disability.

So, back to the differences. In the U.S., the Federal Food, Drug, and Cosmetic Act (FD&C Act) is the law enacted by Congress that gave the Food and Drug Administration (FDA) its power. Just as with a delegation-of-authority log in our research activities, Congress delegated the FDA the ability to create regulations within the confines of the FD&C Act, and those regulations are treated as law.

FDA "guidance," however, describes the agency's current thinking on a regulatory issue. Guidance is not law, but to be safe, everyone treats guidance as law, anyway.

Here Come the Caveats

All this sounds simple, and would again prompt me to question why we have regulatory compliance professionals. I should easily be able to go to the FDA website and find out exactly what I should do in this black-and-white world. Right?

Well, here's an example of where things get hugely difficult. There are corporate laws governing how businesses can interact and associate. These govern, for example, the transactions that can take place between a pharmaceutical company, a hospital system, and a physician's research. They also govern what structures will have to be in place in order for these transactions to occur.

Then there are laws such as the Health Insurance Portability and Accountability Act's (HIPAA's) Privacy Rule, the Anti-Kickback Statute, and the Stark Law, which also have influence over what can and cannot happen, or more appropriately, under what circumstances and structures the relationship can happen.

Then there are the FDA regulations (which as I said, are the same as law); the Office of Inspector General (OIG) regulations (which are the same as law); and then the guidance that comes out of the FDA, but also out of the National Institutes of Health and the Office for Civil Rights; along with guidance from dozens or hundreds of other offices.

So what does all this look like? In my mind, it looks like a scatter plot of a random distribution. When I'm feeling more rational, it looks like a Venn diagram with a tiny area of overlap where we can successfully conduct research, improve healthcare, and transact business. Finding that tiny area of overlap where we're in compliance with all these laws, regulations, and guidance can be tough. Sometimes, it's impossible.

In Closing

All these laws, regulations, and guidance are built with the best of intentions, and they all end with unintended consequences. Then we create more laws to try and take care of the unintended consequences. The OIG Safe Harbor Regulation would be an example; check out www.hhs.gov/ohrp/sachrp/appendixc.html regarding concerns that HIPAA would seriously undermine recruitment efforts and make it nearly impossible for researchers to identify and contact potential research subjects.

Within the Department Health and Human Services (HHS) is the Office for Human Research Protections (OHRP), and within OHRP is the Secretary's Advisory Committee on Human Research Protections (SACHRP). As posted on the HHS website, the SACHRP readily acknowledges the confusion that has been created by the overlap of unintended consequences.

So hug a regulatory compliance professional today. They have a hard job.

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Stuart Horowitz, PhD, MBA

Meeting *Global Standards* for Human Research Protections

This issue of *Clinical Researcher* focuses on the global nature of research and the reasons for, and attendant challenges to, conducting clinical trials around our planet. Although humankind is one species sharing the overwhelming majority of what defines "humanness," its members are also different from one another.

Sure, we are all *Homo sapiens,* but we have obvious phenotypic polymorphisms, more subtle cultural differences, and fundamentally, small but sometimes important genetic variability. All are related, as is our history of geographic isolation (despite the advent of air travel). Because of these differences, a cure for one population may not be a cure for all.

Yet our industry is about finding the solutions—hopefully the cures—for what ails us. These are our stated endpoints, and the goals upon which all clinical research professionals ideally are focused. However, in the quest for cures, we cannot help but ask: Do the ends justify the means? Of course not.

For instance, although it may be faster, easier, and less expensive to do research on people without having an independent ethical committee review the research plan, our industry insists on a process of prior independent ethical review. In this way, research is conducted according to ethical principles articulated in the Declaration of Helsinki[1] and the Belmont Report,[2] in which the rights and welfare of subjects are protected through the processes of independent ethics review and informed consent.

Can Research Ethics be Universal?

If populations are culturally different, could it be possible to adhere to one set of ethical principles for the conduct of human research? We think so. In particular, the Association for the Accreditation of Human Research Protection Programs[3] (AAHRPP) has developed a set of standards designed to be applicable internationally and across cultural boundaries.

If populations are culturally different, could it be possible to adhere to one set of ethical principles for the conduct of human research?

Fundamental to the standards is the concept of the Human Research Protection Program (HRPP). An HRPP is a collaborative undertaking of three components:

- organizations that conduct and supervise research, such as hospitals, sponsors, universities, and contract research organizations;
- ethics review committees, such as institutional review boards (IRBs), research ethics boards, and independent ethics committees; and
- investigators and their research staff.

All are guided by the ethical principles governing research.

The AAHRPP standards were designed to provide flexibility in the application of ethical research principles, based on the understanding that although the principles are constant, their implementation needs to be guided by how those principles are practiced locally.

The adoption of a global gold standard for research ethics is not new. Laboratory animal researchers recognized long ago that a single standard makes good sense and is achievable. Accordingly, the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)[4] has established the *de facto* standards for animal research worldwide. Moreover, the National Institutes of Health's (NIH's) Office of Laboratory Animal Welfare accepts AAALAC standards for federally funded investigators, and AAALAC accreditation is specifically noted on the NIH Grant Face Page.

However, human research has lagged in this area. Despite AAHRPP having been active for more than a dozen years, neither the U.S. Food and Drug Administration nor the Office for Human Research Protections within the Department of Health and Human Services recognizes AAHRPP or its standards. Further, AAHRPP accreditation has not yet achieved widespread adoption, with only about 200 organizations worldwide having obtained accreditation,[3] representing less than 1% of all organizations that conduct and oversee research worldwide.

Hope on the Horizon

Despite this laggard behavior, our industry's view of human research can catch up to, and perhaps surpass, what has been accomplished with animal research.

For example, Pfizer, the world's largest biosciences company, was accredited by AAHRPP in 2013. As part of the organization's accreditation, the review and oversight of all its research—worldwide—must meet AAHRPP standards. Pfizer has voluntarily agreed that research in any country (even in those without an accredited IRB) will meet the minimum standards of review through an accredited IRB.[5]

What prevents organizations from seeking AAHRPP accreditation? Many organizations claim to see no value in AAHRPP accreditation, that the cost of accreditation exceeds any benefit, that accreditation is about paperwork and not practice, and that their organization upholds high ethical standards without having to be accredited. However, my experience in working with research institutions is that few organizations can meet AAHRPP accreditation standards without making changes to their processes.

Research organizations that focus on practice get accredited, whereas research organizations that polish their paperwork without considering practice struggle to achieve accreditation. Organizations that see no value in AAHRPP accreditation are discounting the value of improved human subject protections.

Fundamentally, AAHRPP represents a confidential and peer-driven process of self-assessment followed by peer review. To my knowledge, there is no process that is so perfect that it would not benefit from annual internal self-assessment and external independent peer review every three to five years.

True, AAHRPP accreditation requires payment of annual fees, but those annual fees are small compared to the cost of hiring a consultant to conduct the same depth of review. Organizations that achieve accreditation uniformly experience improvements in their ability to uphold ethical standards of research and improve human subject protections.

Conclusion

Our industry is based on the trust of human subjects, and that trust is maintained by conducting research in a manner consistent with high ethical standards.

Our industry should adopt the AAHRPP standards followed by Pfizer and other pioneering research institutions and sites. Our industry should set the goal that every research site, every sponsor, and every contract research organization take a close look at its operations relative to the AAHRPP standards, open itself to peer review by independent external site visitors, and demonstrate its commitment to human subject protections by achieving AAHRPP accreditation.

The time is now.

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Neither the U.S. Food and Drug Administration nor the Office for Human Research Protections within the Department of Health and Human Services recognizes AAHRPP or its standards.

IN MEMORIAM
Felix Gyi, DPharm, MBA

Felix Gyi, CEO and founder of Chesapeake Research Review, LLC (also known as Chesapeake IRB), passed away on October 2, 2014. He was 58 years old, and is survived by his wife and daughter. His unexpected death saddens all who knew him.

Felix A. Khin-Maung-Gyi, was born in Rangoon, Burma. In 1968, at age 12, he and his family moved to the United States. In 1983, Felix earned his bachelor's degree in pharmacy from the University of Maryland School of Pharmacy, and in 1986, he earned a doctorate in pharmacy from Duquesne University. He later earned an MBA from Loyola University in Maryland.

Trained as a pharmacist, Felix began his professional career with a deep understanding of drugs and pharmaceutical regulations. In 1993, after working in pharmacosurveillance, investigational supplies, and regulatory affairs for the pharmaceutical industry with Fidia Pharmaceutical Corp, Felix founded Chesapeake IRB, where he remained until his death.

Felix was not only an executive business leader, he was also an educator and an ethicist. He coauthored the book *Ethics of the Use of Human Subjects In Research* and wrote chapters in other books, as well as articles in such publications as *The Monitor* (now called *Clinical Researcher*), *DIA Journal* (now called *Therapeutic Innovation and Regulatory Science*), and *Applied Clinical Trials*. For years he served as an editorial advisor for the *Clinical Trials Advisor*. In 2003, he began a term serving on the Secretary's Advisory Committee on Human Research Protections, advising the U.S. Secretary of Health and Human Services. From 1988 to 1998, he was adjunct assistant professor in healthcare services at George Washington University.

Felix was passionate about the protection of human subjects. This was evidenced not only by his written works and public service, but also by his frequent public presentations. Of particular note, for the last few years he participated in the best attended panel discussions at the annual ACRP Global Conference & Exhibition. It wasn't just that he drew a large audience; he collaborated with the other panel members to keep the presentation fresh and relevant year after year.

Collaboration and mentorship were the hallmarks of Felix's career. All who have worked with him remark on how much they learned during their time with him. As a mentor, Felix felt close to trainees, even to those who advanced and left Chesapeake for other positions. If you didn't know Felix personally, it is still possible to know him through these people serving various positions in research and healthcare.

For them and for the rest of us, Felix will be sorely missed.

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20 YEARS of South African Democracy:

Transformation and Progress in Clinical Research

PEER REVIEWED | Suheila Abdul-Karrim, BSc, CCRA, CCRT, MICR CSci

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South Africans have been celebrating 20 years of democracy and freedom in their country in 2014. The past two decades have brought a transformation to the nation across many sectors of public and private life: Once denigrated and sanctioned, South Africa is now an internationally recognized destination for many business enterprises, including those tied to clinical research. [A closer look at the history behind these developments can be found in this author's article, "Keeping the Ball Rolling: Clinical Trials in South Africa," in the February 2012 issue of *The Monitor*.]

From a system of asymmetrical power, South Africa moved toward a culture of integration and unity. To quote the late human rights icon, Nelson Mandela, "To deny people their human rights is to challenge their very humanity."[1]

This paper presents an overview of how clinical research has evolved and prospered in South Africa's modern period of democracy, lists some of the challenges still facing the enterprise, and considers a possible future scenario for regulation of the conduct of clinical trials in the nation.

Background

The constitution of 1996 laid the foundation for the value of human dignity and human rights in South Africa. Even the concept of informed consent for clinical trials is embodied in this constitution, which states: "Everyone has the right to bodily and psychological integrity, which includes the right … not to be subjected to medical or scientific experiments without their informed consent."[2] Hence, clinical trials conducted without adequate informed consent are regarded not only as unethical, but as unconstitutional as well.

The South African regulatory system has made key strides in the protection of clinical trial participants since the emergence of democracy. South Africa has a well-recognized clinical research industry, with a diverse population, broad disease base, and high-quality data being some of the attractions. The conduct of clinical trials is strictly governed by a variety of regulations and guidelines—such as the Declaration of Helsinki, the portions of the *Code of Federal Regulations* pertaining to the U.S. Food and Drug Administration, the European Directive, and the International Conference on Harmonization Guideline for Good Clinical Practice (ICH GCP)—and by local regulations, such as Good Clinical Practice in the Conduct of Clinical Trials in Human Participants in South Africa.[3]

Clinical trials are conducted in both the private and the public sector, but all trials are subject to review and approval by the competent authority known as the Medicines Control Council (MCC) and a research ethics committee (REC).

Ethics

The National Health Act from 2003 (Act 61) stipulates that all clinical research conducted in South Africa must be approved by an REC. Most higher education and research institutions, and even some of the large service-rendering health institutions, have RECs that are responsible for ethical review of research protocols.[4] In fact, there are more than 30 RECs in the country.

All RECs are required to register with the National Health Research Ethics Council (NHREC), which was established as a statutory body under the National Health Act in 2006, and serves as an entity that advises the Department of Health on the management of research ethics. The NHREC's activities include auditing and accrediting RECs, as well as setting norms and standards for conducting clinical trials.

In 2012, the NHREC undertook an audit on 22 registered South African RECs,[5] and found that, overall, most functioned at a reasonable level, but there was a lot of room for improvement. The following recommendations emerged from these audits[6]:

- All RECs should have [standard operating procedures (SOPs)] for guidance or operations and also to ensure the guidelines are adhered to. SOPs should be approved and signed by the relevant authorities.
- Recruitment and appointment of REC members should be revisited.
- All REC members should be given appointment letters including assurance of legal protection.
- Appointment of lay members should be addressed as a matter of urgency.
- NHREC should consider support of RECs in terms of manpower resources and capacity building.
- REC guidelines should be explicit in terms of the constitution of a quorum.
- All REC members should receive training during induction and continuously thereafter.
- Monitoring of research should be done consistently by RECs.
- RECs should have a system in place to handle complaints.

Research on human subjects in South Africa is guided by the South African Good Clinical Practice (SA-GCP) guideline, which was published by the Department of Health in 2000 and revised in 2006. This guideline was incorporated into the 2003 National Health Act, which also legally enforces compliance with ICH GCP and Declaration of Helsinki.[7] RECs must adhere to these guidelines when evaluating clinical trials; the primary responsibility of the REC is the protection of research participants.

Competent Authority

Established under the Medicines and Related Substances Act (101) of 1965, the MCC is the competent authority for overseeing the regulation of medicines in South Africa, and is also responsible for the approval, inspection, and oversight of clinical trials in South Africa.

The MCC operates through a Registrar of Medicines and 11 technical expert committees. One of them is the Clinical Trials Committee (CTC), comprised of external experts from various institutions across the country. In accordance with SA-GCP's

TABLE 1: MCC Approval Categories

Approval Code	Explanation
1a	Approval
1b	REC approval outstanding
2a	Outstanding issues can be dealt with in-house
2b	Outstanding issues must be checked by original reviewer
3	Original reviewer reports back to full committee
4	Referral for specialist opinion
5	Rejection of application requires full resubmission if to be reconsidered
6	Rejection because of missing component(s)

evaluation checklist for clinical trials, the CTC's review of an application should include "previous research relating to safety and potential benefit of intervention,"[8] assessment of trial methods, and consideration of ethical issues. After the review process, applications are categorized into levels of approval (see Table 1).

Once approval is received, the approval document serves as a permit for importing study medication. For biological samples (blood, tissue, etc.) being sent out of the country for analysis, an export permit is required.

Reports on the progress of the study are sent to the MCC every six months from the date of approval. These reports include information on the study status (recruitment, enrollment), safety aspects (all study-specific serious adverse events, adverse events occurring in South Africa, and listings of all suspected unexpected serious adverse reactions occurring globally for the investigational product), and protocol deviations.

After approval, all clinical trials must be registered on the South African National Clinical Trials Register (SANCTR) (see Figure 1), which provides the public with updated information on clinical trials on human participants being conducted in South Africa.[9] The SANCTR covers more than 1,900 registered trials, with those devoted to oncology, infectious diseases, cardiovascular conditions, and metabolic diseases dominating the research field (see Table 2).

TABLE 2: Clinical Trials Being Conducted in South Africa[9]

Disease Area	Number
Bacterial and Fungal Diseases	861
Behavioral and Mental Disorders	68
Blood and Lymph Conditions	25
Cancers and Other Neoplasms	126
Crohn's Disease	3
Conditions of the Urinary Tract and Sexual Organs, and Pregnancy	44
Digestive System Diseases	36
Diseases and Abnormalities at or Before Birth	6
Ear, Nose, and Throat Diseases	7
Eye Diseases	10
Gland- and Hormone-Related Diseases	29
Heart and Blood Vessel Diseases	125
Immune System Diseases	98
Injuries, Poisonings, and Occupational Diseases	6
Muscle, Bone, and Cartilage Diseases	46
Nervous System Diseases	41
Nutritional and Metabolic Diseases	124
Parasitic Diseases	1
Rare Diseases	15
Rheumatoid Arthritis	4
Respiratory Tract	108
Skin and Connective Tissue Diseases	23
Symptoms and General Pathology	17
Viral Diseases	92
Other	4

Challenges

Despite the processes in place, the MCC has had significant setbacks in the last decade. For example, there have been long delays in approval time for clinical trials and issuing of export permits. There are also no final regulations for clinical trials on medical devices in South Africa.

Such problems are attributed to a lack of capacity and resources within the MCC. According to

Clinical trials are conducted in both the private and the public sector, but all trials are subject to review and approval by the competent authority known as the Medicines Control Council and a research ethics committee.

FIGURE 1: Overall Approval Process for Clinical Trials

one source, "The reviewers who advise the Health Minister on whether or not a product is safe and effective are not full-time employees of the South African government. As a result the councils that review clinical trial and drug registration applications only meet every few months. This results in clinical trial and drug registration approval times that are longer."[10]

The delay in approval (sometimes up to 10 months) puts South African clinical trial sites at a disadvantage by leading to shorter recruitment periods. Although sites have met their minimum recruitment targets and maintained South Africa's reputation for efficient enrollment in limited timeframes, it seems likely that enrollment could often be much higher if trials were approved earlier.

The Department of Health conducted a review following complaints about the lengthy timeframes for approval of clinical trials and the fragmentary operational systems of the MCC. "In recognition of this issue, the South African Health Minister submitted new regulatory legislation in 2008. The Parliament of South Africa passed the legislation [that] would create a new regulatory agency, the South African Health Products Regulatory Agency or SAHPRA."[10]

To the dismay of the pharmaceutical industry, "SAHPRA has been stuck in the works for years."[11] Proposed amendments to the Medicines and Related Substances Act were not implemented, and the bill was subsequently redrafted over a period of more than a year. The bill includes measures to reduce the registration time for medicines and medical devices through mutual recognition agreements with other regulatory agencies in the U.S. and U.K.

Despite the processes in place, the MCC has had significant setbacks in the last decade. For example, there have been long delays in approval time for clinical trials and issuing of export permits.

The Way Forward

In March 2014, the Medicines and Related Substances Amendment bill was tabled in parliament. The goal of the bill is to replace the existing Medicines Control Council with SAHPRA. As noted in news coverage:

> This is the government's second attempt at enabling legislation for SAHPRA, after it failed to enact amendments to the Medicines and Related Substances Act in 2008 due to technical problems. One of the key changes in the bill is a new governance structure in which SAHPRA's CEO will have the authority to appoint technical committees, and will report to a board of between 10 and 15 experts appointed by the

health minister. The previous version had a CEO appointed by the health minister, with the minister given final authority for the approval of new products, a structure critics argued would have left the agency vulnerable to political interference.[12]

The new body will have a wider scope and will review aspects that had gone unregulated, such as medical devices and complementary medicines. With the legislation of SAHPRA, several device provisions will be created. "SAHPRA will have the power and be mandated to evaluate all medicines, medical devices, and other health products with medicines or medical content for efficacy, safety and quality."[13] SAHPRA will also be responsible for food, cosmetics, and diagnostics.

The proposed transition from MCC to SAHPRA provides an opportunity for a regulatory system in which operational issues are handled adequately. Meanwhile, with the bill tabled in parliament, the clinical research industry looks forward to the functional adoption of this legislation. A process has begun that aims at reducing the disparities with regard to capacity building and infrastructure within the regulatory framework.

In the words of the late Nelson Mandela, "The greatest single challenge facing our globalized world is to combat and eradicate disparities."[14] The building blocks are in place for a comprehensive and efficient regulatory agency with a promising future that will enhance South Africa's current standing in the clinical research arena.

The proposed transition from MCC to SAHPRA provides an opportunity for a regulatory system in which operational issues are handled adequately.

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The New European Clinical Trial Regulation: *Administrative and Operational Changes*

PEER REVIEWED | Regina Freunscht, MSc | Norbert Clemens, MD, PhD, CPI

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European legislation on the clinical research environment was harmonized in 2001 with the implementation of Directive 2001/20/EC, the "Clinical Trial Directive" (CTD)[1] scheduled for 2004, which was finally completed in all 28 member states[2] of the European Union (EU) in 2006. Directives are addressed to national authorities, who must then take action to make them part of national law.

As stated in the CTD, a review of its impact on clinical research in Europe was scheduled five years after its implementation, along with exploration of potential revisions of the legislation. The review, called "Impact on Clinical Research of European Legislation," was a one-year project financed by the European Seventh Framework Programme. The results were presented during a conference in Brussels on December 2, 2008. The conclusions of the meeting have been compiled as a final report[3] to the European Commission.

The review conclusions suggested, for example, a simplification of the clinical trial authorization (CTA) process, harmonized practices in ethics committee requirements, and changes in expedited safety reporting. The CTA includes a submission to national ethics committees and national competent authorities, and a registration of every single clinical trial at the European Clinical Trial Database called EudraCT (details can be found online in Wikipedia[4]). A stunning outcome of the review was that the CTD, aiming to harmonize the legislative environment, resulted in 34 legal acts, 59 application acts, and 29 guidances, which adds up to a total of 122 rules.

As a result, the European Commission drafted a "Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products

for Human Use, and repealing Directive 2001/20/EC." Regulations are the most direct form of EU law; as soon as they are passed, they have binding legal force throughout every member state, on par with national laws.

On May 27, 2014, the *Official Journal of the European Union* published Regulation Number 536/2014 on clinical trials on medicinal products for human use.[5] This regulation was approved by the European Parliament and the Council on April 16, 2014, and repeals the Directive 2001/20/EC with relevance to the European Economic Area (EEA).

This article aims to summarize the most prominent administrative and operational changes stemming from this European clinical trial regulation. A subsequent article (to be submitted to this journal at a later date, when more details are available) will discuss potential consequences resulting from its implementation (with details on low-intervention trials, archival periods, safety provisions, and transparency provisions), once the ongoing necessary national legislative adoptions have been completed (see Figure 1).

The regulation consists of 19 chapters and seven annexes (reference), and covers interventional, national, and multinational clinical trials with medicinal products in the EU, independent of sponsor (industry, noncommercial, academia), and introduces a new category of low-intervention clinical trials. It came into force on July 16, 2014, and shall apply no earlier than May 28, 2016.

Another requirement is the full functionality of both the EU portal and the EU database, which have to be developed by the European Medicines Agency (EMA). This development process has just begun. *De facto,* the regulation will finally come into force in all EEA countries after the EU Commission has been satisfied with the full implementation and functionality of the EU portal and the EU database.

Furthermore, a transition period was granted until May 28, 2017, during which time clinical trial sponsors can decide which studies will be covered by the new Regulation 536/2014 or by the Directive 2001/20/EC. Consequently, it might be the end of May 2019 before all clinical trials in the EEA are being covered by the new regulation.

Abbreviations Used

CTA	Clinical Trial Authorization
CTD	Clinical Trials Directive
EC	Ethics Committee
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database

FIGURE 1: Summary of Administrative, Operational, and Other Changes Imposed by Regulation 536/2014

ADMINISTRATIVE

Regulation
- Binding in its entirety
- Directly applicable in all member states by all stakeholders
- The EU Commission must report after five years to the EU Parliament and the EU Council on application of the Regulation and its impact on scientific and technological progress

Scope
- Interventional, national, and multinational clinical trials with medicinal products in EU independent of sponsor (industry, noncommercial, academia)

Role of EU Commission
- Control program: Member states must supervise compliance within EEA, studies conducted outside EU must comply with GCP and equivalent standards for subject rights, safety, and data integrity
- Support member state coordination
- Delegate acts to update provisions in the Annexes on application dossier, safety reporting, labeling, and good manufacturing practice

Role of EMA
- Set up and maintain EU database and portal
- Coordinate inspections

OPERATIONAL

Single Submission Dossier
- One format and content (Annex I/II)

EU Portal/Database by EMA
- For all communication: Sponsor to/from member states and between member states

Assessment
- Part I (general dossier): one joint assessment by reporting member states and member states concerned
- Part II (national dossier): national assessment by reporting member states and member states concerned
- Member states to organize the assessment process by authorities and ethics committees consistent with Regulation

One Single Decision via EU Portal
- By each concerned member state on Part I and II
- Defined opt-out mechanisms for member states from joint Part I assessment

New Member States Concerned and Modifications
- Mechanism for addition of new member states concerned without reassessment by all other member states concerned
- Concept of single submission, coordinated assessment, and decision applied to substantial modifications

OTHER

Transparency Provisions
- Summary of results to be published within one year after end of trial
- Clinical study report to be submitted to database 30 days after grant of marketing authorization

Informed Consent
- Strengthened provisions
- Maintenance of specific existing national provisions

Safety Provisions
- Streamlined provisions
- Sponsor direct reporting into EudraVigilance

Changes to the Clinical Trial Authorization (CTA) Procedure

Under the current legal framework, multinational trials within the EEA are reviewed by every individual member state under national auspices, which results in prolonged review timelines of several months for a given trial. Some national authorities (e.g., Spain, Czech Republic) require the translation of the protocol and other essential documents into the local language instead of using the master documentation and translated synopses.

The new process signifies an improvement compared to the current CTA system by offering a one-stop shop and clear *modus operandi.*

The regulation aims for a simplified process for clinical trial approval via a central portal for applications and joint assessments by member states, similar to the current option of a voluntary harmonization procedure for cross-EU CTAs. The main goal is to have a competitive timeline of 60 calendar days for the CTA process, as compared to other regions.

Under the regulation, ethical review will be performed by an independent ethics committee (EC), but all member states shall ensure that this is aligned with the timelines and procedures for CTAs. The timelines currently span from 15 days for Phase I trials in Belgium to 60 days for multicenter trials in several member states.

The new process signifies an improvement compared to the current CTA system by offering a one-stop shop and clear *modus operandi;* however, timelines and the appropriate involvement of ECs need to be monitored closely in order to support the ambitious CTA and EC review timelines across Europe.

Validation of the accuracy and acceptability of a CTA application is coordinated by a reporting member state and shall not take longer than 10 days. Validation of the CTA means checking for completeness and appropriateness of the submitted documentation. The sponsor will apply to the appropriate reporting member state, but the final decision will be made by all member states through the EU portal as the reporting member state consults with all the member states concerned—that is, those additional member states where the sponsor plans to conduct the clinical trial—to drive the assessment of the CTA application.

Within the assessment phase of Part I, the reporting member state will focus on:

- Whether the clinical trial is a low-intervention clinical trial
- Anticipated therapeutic and public health benefits
- Risk and inconveniences for the subjects
- Compliance with the requirements concerning the manufacturing and importation of investigational medicinal products and auxiliary medicinal products
- Compliance with labeling requirements
- Completeness and adequacy of the investigator's brochure

The timelines for this assessment will usually take 45 days—26 days for the initial assessment by the reporting member state, 12 days for the coordinated review of all member states concerned, and seven days for the reporting member state to consolidate all comments received. However, this timeline may be extended to 31 days for requests for additional information from the sponsor, which then has 12 days to provide the requested information, followed by a coordinated review within 12 days, and an additional seven days for the reporting member state to consolidate all comments received.

Within the assessment phase of Part II (by each member state individually), the focus will be on:

- Compliance with the requirements for informed consent
- Compliance with the arrangements for rewarding or compensating investigators and subjects
- Compliance with the arrangements for recruitment of subjects
- Compliance with data protection rules
- Suitability of individuals involved in or conducting a trial
- Suitability of sites
- Damage compensation
- Compliance with rules for the collection, storage, and future use of biological samples of the subject

Each concerned member state may request additional information from the sponsor. The timelines for assessing Part II of the CTA application will take 45 days (aligned with Part I), with a possible extension of another 31 days for a request of additional information (12 days for the sponsor to provide the information followed by 19 days for review by the member states).

Finally, the reporting member state will notify the sponsor (or applicant) with one single decision (including completed EC review) within five days of the reporting date or extended reporting date.

Once the Decision Has Been Made

A concerned member state may not agree to accept Part I of the assessment report on the following grounds:

- Participation in the trial would lead to a subject receiving a treatment that is inferior to what is used in normal clinical practice in this member state; or
- Infringement of the national legislation referred to in Article 86 (specific requirements for special groups of medicinal products, such as medicinal products from human or animal cells, abortifacients, controlled substances, gene therapy clinical trials modifying the subject's germ line genetic identity).

Disagreement with the conclusion of the reporting member state can be based on safety, data reliability, or robustness considerations, and must be communicated via the EU portal (including justification of the disagreement).

A negative conclusion by the reporting member state on the CTA application shall be considered as a negative conclusion by all member states concerned. This could be prevented by early pre-CTA consultation with the reporting member state preferred by the sponsor, which would be comparable to a pre-Investigational New Drug type B meeting procedure with the U.S. Food and Drug Administration.

Furthermore, concerned member states shall refuse to approve the trial if:

- it disagrees with Part I of the reporting member state (opt-out procedure),
- assessment of aspects in Part II are not complied with, or
- a "national" EC has issued a negative opinion.

Changes to the EC Review

ECs are very heterogeneous in Europe. This applies also to the number of committees that are institutionalized in the different European member states; the number varies from just one EC to several hundred.[6] The regulation defines an EC as an independent body that is empowered to give opinions for the purposes of this regulation, to include the views of laypersons, in particular patients or patient organizations. It explicitly requires all member states to organize their ECs to be able to conduct their assessments within the timelines applicable.

A clinical trial approval will not be granted if an EC has issued a negative opinion that is valid for all member states. The regulation calls for a greater collaboration between ECs, and will certainly improve the pace of trial approval as well as provide the potential for networking, collaboration, and convergence of standards in the field. The creation of EC networks will be encouraged.

The EU Portal and Database

The regulation requires the EU to design, validate, implement, and maintain an effective electronic portal and database, which should host documents such as applications (Parts I and II), any substantial and nonsubstantial modifications, and information on the addition of new member states in which a clinical trial should run. The EU portal should function as a single data entry point and interface for the submission and communication of information relating to clinical trials.

The EU database should be seen as the single data repository within the EU, which requires the EMA to avoid duplication between the EU database and the EudraCT/EudraVigilance databases. The future EU database will host all assessment reports of a CTA, the member states' decisions, notifications of any means (e.g., start, temporary halt, early termination), clinical trial results (summary results, lay friendly summary), information concerning benefit-risk balance of a clinical trial, information about serious breaches, and all inspection documents (intention, inspection reports by EU and by third countries).

Since enforcement of the regulation depends on the functionality of the EU portal and the EU database, the EU Commission, the EMA, and the EU member states need to agree on clear timelines and milestones, ideally with early consultation of all relevant stakeholders, to avoid any delay in application of the new legal framework and to facilitate its implementation.

FIGURE 2: Clinical Trial Authorization Procedure

Three Steps of Clinical Trial Authorization

Validation (Art. 5)

Assessment Part I (Art. 6) and Part II (Art. 7)

Note: The Regulation does not make any proposal as to the division of roles and responsibilities between competent authorities and ethics committees. This is left up to the member states to organize the attribution of tasks to different bodies within each country.

Decision (Art. 8)

*Medicinal products developed by biotechnological processes. All days are calendar days.

Conclusion

As mentioned earlier, full implementation of the regulation was planned by May 2016, but development of the EU portal and discussion of the legislative aspects within the 28 member states has just begun, therefore implementation beyond 2017 seems feasible. We will continue to monitor the progress of the implementation phase/steps. Once fully implemented, the regulation will decrease the approval times for clinical trials and will increase the speed of clinical research within the EU.

Acknowledgments

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Do Not Discard Until...?

In this issue's column, the questions focus on an important and often confusing issue in clinical trials—namely, study documentation and records retention. There seems to be a lot of confusion on what documents need to be retained and, once the study is complete, how long and where to store them. The advent of the use of electronic technology has facilitated the ability to keep these records as electronic files stored on a site's, sponsor company's, or contract research organization's (CRO's) server, but the question remains: How long should they be stored?

Q: U.S. Food and Drug Administration (FDA) regulations require clinical investigators to retain study-related records and reports for specific periods. However, the regulations say nothing about standards for protecting these records. Does a site need to use fireproof or locked cabinets, or any related standards, to preserve and maintain the physical security of study records?

A: The FDA has stated informally that "the regulations are essentially silent on the topic of physical security for subject information." There is also plenty of regulation and guidance under the Health Insurance Portability and Accountability Act (HIPAA) on the need to protect subjects' confidentiality (through the use of unique identifier codes), but there is little advice on physical measures to maintain record confidentiality. For example, there is no specific requirement in the regulations for locked or fireproof cabinets to store clinical trial records.

The agency leaves it to the regulated parties (sponsors and investigators) to determine the steps necessary to meet this requirement. In fact, the only mention of locked cabinets in the Investigational New Drug (IND) regulations is in the *Code of Federal Regulations* at 21 CFR §312.69 for the storage of investigational drugs that are also subject to the Controlled Substances Act. It is probably best to consult with the sponsor and the applicable institutional review board for recommendations on this topic.

Q: Are there any FDA or good clinical practice (GCP) standards pertaining to the existence or contents of a sponsor's "central file" (or "trial master file" [TMF]), which typically is the file containing all the key documents related to a clinical study?

A: At a recent meeting in response to this question, the FDA stated that "there is no regulatory definition of 'central files' or 'trial master file' in regulations governing [GCP]." The FDA regulations do specify certain records and reports that sponsors and investigators must maintain (21 CFR, Subpart D), and how long these records must be maintained by the sponsor (21 CFR §312.57(c)) and at the site (21 CFR §312.62(c)). However, the regulations do not prescribe where or how the records and reports are to be kept, only that they be retained and available for inspection.

This differs from Europe and other regions, where the maintenance of a formal TMF with these study-related documents is required by regulation (Directive 2005/28/EC and the related guidance in Volume 10 of the rules governing medicinal products in the European Union).

The International Conference on Harmonization (ICH) E6 Guidance for Industry Good Clinical Practice: Consolidated Guidance does make some recommendations in Section 8 about the types of trials records to be maintained and their location (i.e., which records should be kept in the sponsor's or investigator's files). As long as these records are

Do you have a GCP question or an issue that has come up at your site or company? If you are not sure of how to proceed, please send an e-mail to: gcp@moriahconsultants.com and I will answer it in an upcoming column.

adequately prepared, maintained, and retained pursuant to the regulations, they may be stored in any number of ways. One should refer to the protocol and the sponsor/CRO's specific requirements for which records need to be collected and maintained to support the conduct of the study, and where/how they should be stored.

Q: Keeping with the theme of records retention, what is the recommended course of action for an investigator if he/she retires and no longer has the ability to store source data and essential documents from a clinical trial?

A: According to 21 CFR §312.62, "An investigator shall retain records required to be maintained under this part for a period of [two] years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until [two] years after the investigation is discontinued and FDA is notified." There is similar language in 21 CFR §812 for medical device clinical trials.

If an investigator retires and is unable to store the study data, he/she must transfer custody to another person who will accept this responsibility. The investigator should provide a written notice of this transfer to the sponsor. The Investigational Device Exemption regulations specially address the option of the transfer of custody of records in 21 CFR §812.145(e); however, IND regulations do not discuss the transfer of custody (21 CFR 312.57), even if it is often done. This notification should be maintained in the investigator file.

Sites can also consider placing the files in a central warehouse, rather than in storage more immediate to the investigator. Most commercial storage facilities are secure, temperature controlled, and capable of bar code labeling for easy access to materials when requested. Although the tactic may be associated with annual storage costs, for industry-sponsored studies, this can be added as a line item to the budget to offset the costs the institute may bear to ensure the documents are retained for the required time period.

Q: On a related question, how does an investigator address this requirement if his/her institution has a policy of destroying records after a period of time that is shorter than the time period mandated by the FDA?

A: If an investigator is conducting a study at an institution that will otherwise destroy records before the FDA-mandated record-retention period, then the investigator must request that the institution make an exception to its policy to honor the requisite record-maintenance period. In other cases, the sponsor might provide for offsite storage of the study records. In all cases, an investigator should be reminded not to destroy any study records without first checking with the sponsor. The FDA's expectations for storage do not change just because an institution has another policy.

Q: So, how does a site handle study records retention and destruction when attempts to contact the sponsor after some designated time reveal that the sponsor went out of business?

A: If a site attempts to contact a sponsor at the appropriate time regarding study records and can't locate anyone (due to being out of business), I would recommend that the site have an internal institution policy (which aligns with the state requirements) on record retention. If a site can show that it exercised due diligence in trying to contact the last known sponsor over several months and via several different forms of communication, including things like certified letters, phone logs, e-mails, Google search failures, etc., without success, a site can default to its own policy. In this case, as long as a site is meeting institution policy and state law regarding health records, it would probably be acceptable to all concerned parties, including the FDA.

If an investigator retires and is unable to store the study data, he/she must transfer custody to another person who will accept this responsibility.

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Photo: Ogata/TOYOKEIZAI

Regulations and Credibility of Phase IV Clinical Trials: Lessons from the Japanese Valsartan Scandal

PEER REVIEWED

Chieko Kurihara, BSocSc

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Phase IV clinical trials are postmarketing studies vital to establish longer term, additional clinical evidence in the general population under regular usage conditions. They provide more pragmatic information on the safety and effectiveness of drugs than premarketing clinical trials involving selectively recruited subjects.

Sometimes, however, drug companies use Phase IV studies as marketing tools to increase sales by generating biased favorable evidence for their own products.

This article outlines the Japanese "valsartan scandal" as an example of abuse of Phase IV studies, and it provides a comparative analysis of regulations for Phase IV clinical trials among the pharmaceutical-producing nations of Japan, the United States (U.S.), and the collective European Union (EU), as well as South Korea and Taiwan. The article then concludes with an argument for the necessity of establishing an international accreditation system of clinical excellence.

Left: Novartis leadership (Japanese) bowing in apology for the valsartan scandal
Right: Novartis leadership (Western) bowing in apology for another drug scandal

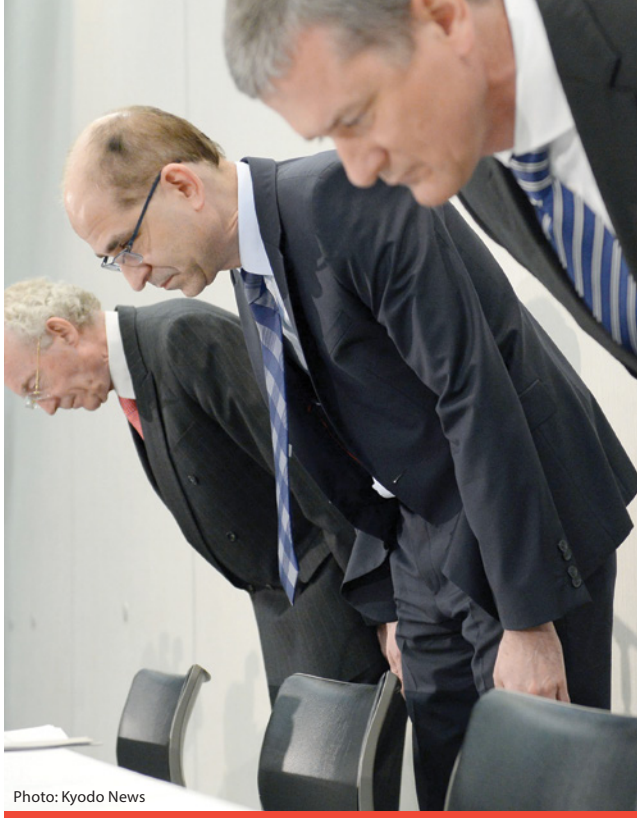

Photo: Kyodo News

Valsartan Scandal in Japan

Soon after the marketing authorization of valsartan (Diovan®), five universities conducted large-scale multicenter clinical trials demonstrating valsartan, an angiotensin II receptor blocker (ARB), as being superior to various non-ARBs in terms of cardiovascular event prevention or improvement of laboratory data related to renal function.[1-5] These results were used extensively for promotion by the distributor company, Novartis Pharma KK, the Japanese subsidiary of the Switzerland-based Novartis.

All of the studies adopted a design using "prospective randomized open blinded endpoints" (PROBEs).[6] Novartis had donated unrestricted money to the five universities totaling 1.13 billion Japanese yen (JPY) (approximately 11 million USD) from 2002 until 2014. Nobuo Shirahashi, a former employee of Novartis, and his colleague conducted statistical analysis of these five trials.

"Concerns" about three of the five trials were published in *The Lancet* in April 2012,[7] saying it was "odd" (i.e., questionable) that the mean and standard deviation of baseline and achieved systolic blood pressure were almost the same among the valsartan and control groups in the three trials. The article author continued that the significant effectiveness of valsartan found was inconsistent with other ARB trials and with the author's impression from his own clinical practice.

Following intensive debates of academic societies and newspaper criticisms revealing that a Novartis statistician supported these studies without properly disclosing his affiliation with the company, the Ministry of Health, Labor, and Welfare (MHLW) of Japan set up a board of inquiry and the five universities investigated the related case records. Consequently, four of the five concluded the possibility of data manipulation.

Scientific articles from three of the universities were retracted.[1-3] Another university recommended retraction, but the investigators declined to comply. The MHLW accused the sponsor company of exaggerated claims in violation of the Pharmaceutical Affairs Law (PAL). The Tokyo District Public Prosecutor's Office has since investigated the company and the universities.

Eventually Shirahashi was arrested and charged with falsifying clinical trial data[8] used in exaggerated advertisements of the drug, and in the following month, the company was accused as the employer, according to the dual punishment rule. If Shirahashi and/or Novartis were found guilty, the maximum fine would be 2 million JPY and two years in prison. Sales of the drug, which had been about 108 billion JPY in 2012, decreased 15.7% from July to September of 2013, presumably as a result of the impact of the scandal.[9]

Lack of Regulations and Education in Japan

The news headlines following the valsartan scandal have revealed other cases of cozy relationships between clinical researchers and drug companies, most involving excessive company assistance to investigator-initiated trials (IITs) of marketed drugs.

Another prominent case involves another ARB, candesartan (Blopress®), from Japanese giant Takeda Pharmaceutical Company Limited. Slightly different graphs devoted to research results were found in the original article[10] about the drug and in its promotional material,[11] with the latter showing the so-called "golden cross" (crossing of Kaplan-Meier curves of comparative groups) indicating the merit of candesartan. Takeda gave 3.75 billion JPY to one university and provided assistance from study startup to publication of the findings, falsely telling the public that it had not given such assistance.

Why has such collusion happened in Japan? The risk factors of the valsartan trials are summarized in the chart; there are two aspects of the peculiar background situations. First, the Japanese GCP (Good Clinical Practice) Ordinance[12] under the PAL regulates only clinical trials aimed at marketing authorization of new drugs or new indications.

When researchers seek partial coverage of public health insurance, they apply to the Advanced Medicare Care Program under the Health Insurance Act. All other types of clinical research are covered by governmental ethical guidelines[13], which are not legally binding (Table 1). These guidelines permit researchers to start a clinical trial without first gaining regulatory approval; they just need their institution's permission, based on the ethics committee's authorization. Therefore, regulators

A Culture of Honor

When a Japanese company or university is found to be unjust, the leadership apologizes with a formal bow in front of the press and television cameras. This practice is common with Japanese leaders, but rare for Western leaders. When a subsequent drug scandal was found to be unlawful, which caused the change of Novartis leadership from Japanese to Western, the public bow of apology was still required by the Japanese culture of honor.

Risk Factors of the Phase IV Clinical Trials of Valsartan Mentioned in this Article

POINTS TO BE CLASSIFIED AS LOW RISK

Safety and efficacy of the investigational drugs

- All of the test drug and controls are the approved ones with established therapeutic evidence.
- Usage of the drug is in the range of authorized label claims.

Patient population

- Not categorized as vulnerable population (capable patients with hypertension, excluding women who may become pregnant).

POINTS TO BE CLASSIFIED AS HIGH RISK

Geography

- In Japan there are no legally binding GCP regulations for Phase IV of IITs.

Human resource

- Clinical investigators were not knowledgeable about biostatistics and clinical trial management.
- Biostatistician was not qualified in biostatistics and was employed in the promotional unit of the funding company, which was the provider of the test drug.
- No qualification system existed for project management staff or ethics committee members.
- None of them was knowledgeable about conflict-of-interest management.

Clinical trial design

- PROBE design using soft endpoints easily biased with subjective evaluation.

Computerization

- There was no electronic data capture system, and the staff were not well trained about electronic data input.
- Data management center was independent, but the responsible person was a former junior staff member of the above-mentioned biostatistician when they were in another company (not Novartis).
- Statistical data analysis was conducted on the above-mentioned biostatistician's personal computer for private use.

Funding

- The funding company was the provider of the test drug, and had a strong wish to advertise the drug as being superior to other competitive drugs.

neither review the protocol nor inspect the research, and monitoring and auditing are not required.

Subsequent to the valsartan scandal, MHLW proposed drafting revisions to the clinical research guidelines to include the requirement of monitoring and audits for the high-risk research category; however, these guidelines are outside of PAL. Because of this huge regulatory gap, there is also a significant gap in the costs between GCP trials and trials under the guidelines. For this reason, companies prefer to fund "quasi" IITs in the framework of clinical research guidelines.

Another problem revealed by the valsartan case is that many clinical researchers in Japan are not well trained in science, ethics, and clinical trial management. Consequently, they are too compliant with drug company sales representatives, who may be more than willing to assist in the trials of their company's products. Furthermore, one of the authors of the retracted valsartan article[1] said that "we are not responsible for data manipulation, because we are not knowledgeable about statistical analysis."[14]

In 2014, a new law to establish a Japan Medicines and Research Development Organization was passed. Learning from the above bitter experiences, as well as from successful cases of government-funded academic research incorporating intensive management programs, this organization integrates entire governmental funding programs in the health area and applies strengthened project management programs to promote innovative research and development. Japan is now coming into a new era of academia-oriented research and development, although it is still far behind the Western world.

Regulations of Phase IV Clinical Trials in the United States (Table 1)

In the U.S., even if a trial is for an approved drug, the Food and Drug Administration (FDA) requires an investigational new drug application (IND) if the applicants intend to make new label claims or promote the new study results.[15] The IND regulations are defined by the *Code of Federal Regulations* (CFR) in 21 CFR 312 and in other areas compatible with GCP (21 CFR 50, 54, 56), under the Food, Drug, and Cosmetic Act.

Even without such an intention, clinical trials at institutions receiving federal research funding are within the scope of 45 CFR 46, titled Protection of Human Subjects, under the National Research Act. Only some researchers at private hospitals not receiving any federal funding can conduct clinical trials outside these CFRs, using an approved drug in the range of the approved label, without intention for new label claims or promotion.

Academic researchers in the U.S. can submit an "investigator IND"[16]; its regulations are not different from those for a company's IND, but the quality control is not as intensive as that of a company's IND. Some of these IITs may be funded by the government and others by companies. Some of this research has generated company-favorable research results, often resulting in public criticism.[17]

Also in the U.S., the cascade of scandals surrounding off-label promotions[18] resulted in the 2007 FDA Amendment Acts,[19] which strengthened risk management throughout the lifecycle of drugs and required clinical trial registration to the public database (ClinicalTrials.gov). In 2013, FDA issued guidance for a risk-based approach to monitoring,[20] which gives instructions for risk identifications (Table 2) and recommends streamlined monitoring for lower risk research and intensive monitoring for higher risk research.

Furthermore, in 2011, the U.S. Department of Health and Human Services proposed a wide range of revisions to the above-mentioned CFRs to enhance the protection of research subjects and to reduce burden, delay, and ambiguity for investigators—in terms of risk-based subject protections, streamlined institutional review board oversight of multisite studies, improved informed consent,

data protections, data collection to enhance system oversight, extension of federal regulations, and harmonized regulations through federal agencies.[21]

In such a regulatory reformation environment, nearly 200 institutions (mostly in the U.S., including the National Institutes of Health, and some outside but collaborating with U.S. institutions) received accreditations from the Association for the Accreditation of Human Research Protection Programs (AAHRPP),[22] a nonprofit organization established in the U.S. in 2001. AAHRPP accredits the human research protection program of its member institutions to be compliant with U.S. regulations toward promotion of excellent, ethically sound research. Also, the Association of Clinical Research Professionals[23] is an educational organization that offers certification programs for principal investigators and other clinical research staff. Further, in 2011, the Alliance for Clinical Research Excellence and Safety (ACRES)[24] was established to network all stakeholders, including regulatory authorities, in the world to provide education and accreditation programs.

Regulations of Phase IV Clinical Trials in Europe (Table 1)

In Europe, the Council of Europe drafted the Convention on Human Rights and Biomedicine in 1997[25] and the Additional Protocol concerning biomedical research in 2005,[26] which called for legal protection of human research subjects.

In 2001, the EU issued the Clinical Trial Directive,[27], which was implemented in 2004 and covers clinical trials of approved or unapproved drugs to be conducted in a GCP regulatory framework (now covering 28 EU member states). This expansion of regulations was complained about as the cause of the increased cost and burden of IITs.

Through several stages of discussion, in April 2014 EU regulators repealed the Directive and adopted a new Regulation to be implemented in 2016.[28] Some of the research communities sought to exclude clinical trials using approved drugs from the scope of the regulations, but finally such trials were included but categorized as "low-intervention clinical trials," according to the Organization for Economic Cooperation and Development's recommendation for facilitating noncommercial research.[29]

In the Regulation, "low-intervention clinical trials" should fulfill three conditions:

- Investigational medicinal products (IMPs), excluding placebos, are authorized;
- Use of IMPs are in accordance with marketing authorization or supported by evidence in any of the member states concerned; and
- Additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the subjects compared to normal clinical practice.

For low-intervention clinical trials, administrative process, including monitoring and informed consent procedures, may be simplified.

The Regulations do not provide detailed risk-identification viewpoints, but the European Medicines Agency (EMA) in 2013 issued a reflection paper on risk-based quality management,[30] providing more detailed instructions (Table 2). Also, within the European Innovative Medicines Initiative, the PharmaTrain[31] project was started in 2009 to provide diploma courses and master programs for pharmaceutical medicine. This project received €7 million (9 million USD) in support from the European Commission and European Federation of Pharmaceutical Industries and Associations companies.

Regulations for Phase IV Clinical Trials in South Korea and Taiwan (Table 1)

Recently, South Korea and Taiwan developed new Acts to cover the whole range of research involving human subjects, casting a wider scope than the GCP regulatory framework. In South Korea and Taiwan, the scope of the GCP regulation is almost the same as the one in the U.S. and EU, and broader than in Japan.

The Korean Bioethics and Safety Act[32,33] was first developed in 2005 to regulate advanced medical technologies, such as human embryonic and genetic research, just after the first publication of stem cell establishment from a human cloned embryo. However, this report was soon called into question and determined to be a fabrication in January 2006.[34] Through the debates surrounding this issue, South Korean regulators expanded the scope of this Act to cover all research involving human subjects and the Biobank project.[33]

The news headlines following the valsartan scandal have revealed other cases of cozy relationships between clinical researchers and drug companies, most involving excessive company assistance to investigator-initiated trials of marketed drugs.

The retracted papers reporting the valsartan trials

TABLE 1: Comparison of Laws and Regulations Concerning Clinical Trials Focusing on Phase IV Studies

1. **Scope**
2. **Objectives of the regulatory framework**
3. **Characteristics of regulatory framework concerning Phase IV clinical trials**

DRUG-LAW AND GCP REGULATIONS

RESEARCH REGULATIONS OUTSIDE OF GCP

JAPAN

Pharmaceutical Affairs Law and GCP Ordinance

1. Clinical trials aiming at new drug or new indication application. Contains two tracks: company-initiated and physician-initiated clinical trials.
2. Protection of human subjects and scientific integrity of clinical trials for a New Drug Application (NDA).
3. Some of the clinical trials of approved drugs are designated in the Risk Management Plan in the NDA approval. Some of the clinical trials of these categories are conducted under another set of postmarketing survey regulations, but should be compatible with GCP.

Health Insurance Act and Advanced Medical Care Program

1. "Advanced medical care" using unapproved medical technology (drug, device, surgery, or examination, etc.) with health insurance coverage only for the part of accompanied ordinary practice. Some of the drug clinical trials in this framework are required to be compliant with Clinical Research Guidelines or "recommended to consider" about GCP.
2. Medical technology development, partially using health insurance, toward full insurance coverage approval.
3. Clinical trials of an approved drug for new indications are the preferable target of this framework, as more flexible GCP compliance is recommended, although generated data may be insufficient for a new indication application.

Guidelines for Clinical Research (regulatory framework without legal binding)

1. Medical research involving human subjects, including individual identifiable material and data.
2. Human subject protection and promotion of clinical research.
3. Lacking legal force; regulatory permission and inspection; monitoring and audit system; Good Manufacturing Practice and Good Laboratory Practice; mandatory adverse effect reporting, many promotion-driven, company-funded IITs of approved drugs have been studied in this framework.

UNITED STATES

Food, Drug, and Cosmetic Act and 21 *Code of Federal Regulations*

Part 50 Protection of Human Subjects

Part 54 Financial Disclosure by Clinical Investigators

Part 56 Institutional Review Board

Part 312 Investigational New Drug Application (IND)

1. Clinical trial (investigation) using new drugs or authorized drugs.
2. Protection of human subjects and scientific integrity of clinical trials.
3. Clinical trials using an authorized drug without intentions of new label claims and/or promotion may be excluded from or otherwise regulated in this framework in a simplified manner, for which FDA provides "investigator-IND" procedures.

National Research Act and 45 *Code of Federal Regulations*

Part 46 Protection of Human Subjects

1. Any research involving human subjects at the institutes receiving federal funding.
2. Protection of human subjects.
3. Clinical trials using an authorized drug without intention of new label claims or promotion can be conducted under these regulations if the institution receives federal funding; or can be conducted outside of any clinical trial regulations if both investigators and institutions do not receive any federal funding.

EUROPEAN UNION

European Union Clinical Trial Directive (2001/20/EC)/Regulation (No 536/2014)

1. Clinical trial (investigation) using new drugs or authorized drugs.
2. Protection of human subjects and scientific integrity of clinical trials.
3. In the new regulation No 536/2014, regulatory procedures and informed consent requirements of "low-interventional clinical trials" using authorized drugs are simplified.

COUNCIL OF EUROPE

Convention on Human Rights and Biomedicine and Additional Protocol

1. Application of biology and medicine to humans, including research (Convention); and research in the health field involving physical or psychological intervention (Additional Protocol). (Does not apply to research on fetuses and embryos *in vivo*.)
2. Protection of the dignity and identity of human beings and a guarantee to everyone of respect for their integrity and other rights and fundamental freedoms with regard to biology and medicine.
3. 29 of 47 member countries of the Council of Europe are at "entry in force" status and some of these countries have developed laws for protection of human subjects in a wider range than clinical trial regulations.

KOREA

Pharmaceutical Affairs Law and Guideline for Korean GCP

1. Clinical trial (investigation) using new drugs or authorized drugs.
2. Protection of human subjects and scientific integrity of clinical trials.
3. Clinical trials of approved drugs for new indications or new label claims are conducted in this framework.

Bioethics and Safety Act

1. Wide range of research involving human subjects and advanced biomedical technologies, including embryonic research, genetic testing, biobank, and sociobehavioral research.
2. Protection of human dignity, bioethics and safety, public health improvement.
3. Clinical trials of authorized indications of an approved drug may be conducted under the Bioethics and Safety Act rather than GCP framework.

TAIWAN

Medical Care Act; Pharmaceutical Affairs Act and Guideline for Taiwan GCP

1. Medical Care Act and Pharmaceutical Affairs Act (PAA) regulates clinical trials and PAA requires drug trials to be compatible with GCP regardless of intention of NDA.
2. Protection of human subjects and scientific integrity of clinical trials.
3. Clinical trials of approved drugs for new indications or new label claims are conducted in this framework.

Medical Care Act and Human Subjects Research Act and Human Biobank Act

1. Medical Care Act regulates clinical trials and Human Subjects Research Acts cover any kinds of human research including sociobehavioral research. Human Biobank Act regulates biobank projects.
2. Protection of human subjects (Human Subjects Research); to ensure the rights and benefits of participants and to promote medical development and public welfare.
3. Clinical trial of authorized indications of an approved drug is conducted under the Human Subjects Research Act rather than the Medical Care Act.

TABLE 2: Comparison of Risk Identification Viewpoints in the Guidance Documents of the United States and the European Union

U.S. FDA

Complexity of the study design—Higher risk: adaptive designs, stratified designs, complex dose titrations, multiple device placement studies

Types of study endpoints—Higher risk: interpretative, subjective endpoints

Clinical complexity—Higher risk: seriously ill, vulnerable

Geography—Higher risk: differences in standards of medical practice, subject demographics, less established clinical trial infrastructure

Relative experience of the CI (clinical investigator) and of the sponsor with the CI—Higher risk: CIs who lack significant experience in conducting and overseeing investigations; the relative experience of a sponsor with the CI may be a factor in determining an appropriate monitoring plan

Electronic data capture—EDC with capability to assess quality metrics can identify higher risk sites

Relative safety of the investigational product—Higher risk: A product with significant safety concerns or no prior experience in human clinical trials

Stage of the study

Quantity of data—Centralized monitoring may be useful as the quantity of data collected increases

EU EMA

System Level

Organization structures and responsibilities—Organograms, communication plans, contractual partners

Quality system and processes—Standardized procedures

Facilities and computerized systems

Human resources including training and qualifications of personnel

Compliance metrics, performance measurements, quality audit, and/or inspection outcomes

Regulatory and ethical framework

Project Level

IMP

Trial design—Complexity, population (e.g., vulnerability, morbidity), therapeutic area (e.g., recruitment difficulties with rare disease), sample size, eligibility criteria, non-medicinal protocol-related activities (e.g., biopsies), etc.

Operation—Budget, deadlines, staff resource, site selection, contract research organization, supply and infrastructure, databases, reporting and/or communication lines, etc.

Clinical trials of approved drugs conducted in the range of an authorized label may be conducted outside the GCP regulations under South Korea's own version of a Pharmaceutical Affairs Law, but under the Bioethics and Safety Act. Therefore, there is an audit system that is not as strict as conditions found under GCP.

In Taiwan, the Human Research Act[35] was established in 2012 to focus on research not covered by GCP under the Pharmaceutical Affairs Act, and the Biobank Act[36] was established in 2012 to regulate biobank projects. These Acts were developed from the debate over ethically questionable research involving the indigenous peoples of Taiwan.[37]

There is a trend among leading research institutes of these two countries to acquire accreditation from AAHRPP to enable them to be ready for U.S. FDA inspections of clinical trial sites conducting research for global pharmaceutical companies.

Risk-Based Strategies of Phase IV Studies

Research communities around the world are seeking a streamlined regulatory framework for IITs, especially for Phase IV clinical trials, some of which can be categorized as low risk.[20,28-30] The results of Phase IV studies are vitally important, both for public health and for pharmaceutical business. Therefore, we should establish some mechanism to simplify regulations and at the same time generate unbiased, credible research results.

In addition to the risk identification viewpoints presented by the FDA and EMA (Table 2), the valsartan scandal shows that research projects should be regarded as high risk if the investigators are poorly trained and research funds are provided only by the company selling the tested drug. In contrast, the project should be presumed as low risk if the investigators are well trained and research funds are from the government or from two or more companies competing in the therapeutic arena of the drugs being compared in the trial.

The trend is that clinical trials are shifting from large-scale studies generating "one-size-fits-all" evidence of interest to megapharmaceutical companies to personalized medicine studies using strategies of "enrichment"[38] or "adaptive design."[39] These enriched or adaptive trials should be categorized as high risk because of their complexity[20] as well as the possibility of providing the funding company with favorable research results, because these trial designs provide opportunities to breach blinding.

It is crucial to appoint as investigators persons of high professionalism and ethics to manage these newer trial designs independently of the funding organization. If the communities of investigators share high-minded professionalism, then the regulatory procedures and framework could be drastically simplified and streamlined. On the other hand, "protectionism,"[40] or just following the regulations, only damages scientific integrity.

Conclusion

The general principles and regulatory framework for pharmaceutical clinical trials and research involving human subjects are becoming increasingly similar throughout the world (Table 1). Seeking more regulatory reforms toward more detailed and complex regulations within the same paradigm is meaningless.[40]

Now is the time to shift to another mechanism to create a credible community network of "internationally accredited" and excellent institutes, organizations, investigators, and collaborating staff to conduct "credible" Phase IV clinical trials. This kind of global network should be crucially important for the improvement of public health around the world.

Japan is now coming into a new era of academia-oriented research and development, although it is still far behind the Western world.

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An Interview with Liz Wool, CCRA, CMT

I am pleased to feature Liz Wool, CCRA, CMT, as the interviewee for this issue. Liz is another passionate and long-contributing member to the industry, as well as to ACRP. She is the president of QD-Quality and Training Solutions, Inc. (QD-QTS), a clinical research consultancy and training organization based in Nashville, Tenn.

Q: How did you first become interested in clinical research, and can you describe a little bit about the path you took in your clinical research career?

A: In 1978, I began my clinical nursing at Johns Hopkins Hospital (JHH) in Baltimore, Md., with a focus on caring for cardiology patients. At this time, JHH had a robust cardiology research program, and I met many research nurses working on important and exciting clinical trials.

It was during my tenure in the JHH Coronary Care Unit that I had the opportunity to speak to our attending physicians about their research programs, and to the research nurses directly about their role and contributions to the research studies. I was fascinated and inspired to participate in the future innovation of medical care and make a difference for patients in a new role.

Q: Can you tell us a bit more about where you started and the different types of roles you've held?

A: I transitioned from the JHH Coronary Care Unit to become a JHH cardiology research nurse in the mid-1980s, and was assigned to a trial sponsored by the National Institutes of Health (NIH), in which I performed a whole host of clinical research coordinator (CRC) functions.

The most rewarding aspect as a research nurse was caring for the patients and their families, and functioning as both a research nurse and healthcare advocate—assisting them in accessing care and helping them with their post-hospitalization follow-up needs. This position sparked my future desire to expand my experience in clinical research, which led me to work for a sponsor as a clinical research associate (CRA).

My first job in the industry as a CRA was with Baxter Hyland (biologic division) in the early 1990s, monitoring a hemophilia trial that investigated the first Recombinant Factor VIII product (genetically engineered without use of blood products). While I was at Baxter, the product was approved, and this cemented my passion for clinical research and my newly chosen career. This product approval was a compelling innovation and advancement for the care of hemophiliac patients. My career has focused on clinical operations with line management and functional unit management in site monitoring, trial management clinical compliance, quality management, and training for biotech companies, large pharma and biologic companies, and a contract research organization (CRO). Since launching my own company in 2007, I have functioned as a contract in-house CRA and trial manager and trainer. I am often involved in providing training and consulting services in quality compliance operations, standard operating procedure development, training program gap analyses, development and delivery of training curricula and courses, CRO-vendor management, and risk management in clinical trials for sites, academic medical centers (AMCs), U.S. federal agencies, sponsors, and CROs. I have a team of consultants and auditors who work with me supporting the clinical trial enterprise around the globe.

Collaborating with diverse, intelligent, passionate, talented, and committed colleagues who share a unified vision and passion for "excellence in clinical research," continuous learning, and professional growth are among the more notable benefits.

Q: When did you first get involved with ACRP, and what benefits have you reaped from being a member?

A: My involvement with ACRP began at the chapter level in Northern California, volunteering at events at the registration table, serving on the education committee, becoming vice president and finally president of the chapter. On a national level, I have served as a CRA certification exam item writer, on the Membership Committee, and on the Editorial Advisory Board for *The Monitor* (now *Clinical Researcher*).

In December 2013, I completed my four years of service on the ACRP Board of Trustees. Today, I serve on the ACRP Regulatory Affairs Committee and with the ACRP Greater Nashville Chapter. With all of these volunteer opportunities and appointments, the benefits are many: Collaborating with diverse, intelligent, passionate, talented, and committed colleagues who share a unified vision and passion for "excellence in clinical research," continuous learning, and professional growth are among the more notable benefits.

A treasured and unexpected gift from my involvement in ACRP are the lifelong friendships that have been forged through service to ACRP and the clinical research community.

Q: Since your career has spanned many years and you have no doubt seen many changes, what is the most significant change (or top changes) you have seen? How has this affected the industry, either positively or negatively?

A: I can speak to what is both personal and important to me as a professional, with experience dating back to the 1980s. I never dreamed that risk management, quality, and quality management in clinical research would be front and center with the board rooms and executive management of sponsors and CROs, as they are today.

The current focus on equipping and training staff, using a structured, uniform, on-the-job training approach with competence verification/qualification of personnel, is of paramount importance. If implemented, this approach can prevent many isolated and systemic quality issues and errors. This approach is materializing from the shadows of the many effective healthcare organizations already using it within the general healthcare model, into the mainstream of the clinical research industry (sites, AMCs, sponsors, CROs).

In my new role with the Alliance for Clinical Research Excellence and Safety (ACRES),[1] a global nonprofit organization, I am leading a work stream in the development of investigational site standards for professional development of clinical research personnel, which may be used by any type of site, wherever research is being conducted around the globe. Members of ACRES are working collaboratively to create a shared global system that will enable sponsors, regulators, service providers, ethics committees, research sites, and patient subjects to be connected as never before, and to share and more effectively use information across the entire clinical research enterprise, benefiting all stakeholders. Not only is this personally rewarding, but also I believe it exemplifies the importance of, and industry's focus on, quality and safety that will benefit everyone in the clinical research enterprise.

Q: What advice do you have for clinical research professionals, in terms of how to advance their careers?

A: Find your passion! If you don't know, or are having challenges with this, that is okay. I was fortunate to have a number of encouragers and mentors in my career who guided me to a great book (32 years ago!) entitled *What Color is Your Parachute?,* along with The Myers-Briggs™ Type Indicator® personality inventory, and a newer tool, the StrengthsFinder™ assessment, all of which focused me on my abilities and skills, in order to "discover and research" the myriad of jobs and opportunities in the clinical research industry. For example, through a local job search in Maryland, I learned that the U.S. government, through many different agencies, conducts or supports clinical research, which led to a job supporting HIV vaccine research in Thailand with the U.S. Army.

Analyze and identify your innate skills, talents, and aptitudes. What worked for me was a systematic analysis of my "innate skills, aptitudes, and abilities" and matching my passion to those areas of clinical research. Early in my career, I took a supervisory role (an office-based job) in a hospital. I learned the hard way that taking a job because "it would make my resume look better," and one that

did not fit my attributes, was not a path to success after all. Yet, this "non-success" provided the opportunity to learn more about myself for future career paths, to grow in my soft skills, and to find a mentor to help me with situations that I had not encountered before. Specifically, this experience was "turned to good" for others when I encounter people who do not have the ability to do a job the way that is needed. I identify and communicate their talents, skills, and abilities and coach them to other, future roles that would be a better fit. Further, I provide supportive feedback on how to address any performance issues they may be encountering, often relaying my experience, which illustrates that I have been in their shoes, and there is a future for them in clinical research.

Walk with integrity. Never over-represent yourself or inaccurately represent yourself. Since founding my training and consulting firm seven years ago, I have turned down opportunities because I did not have the experience or time to help a potential client. I found that maintaining my integrity has actually brought me business. I credit my parents and my upbringing with instilling this character attribute. I have always embodied it in my career, and advocate that others do so as well.

Q: As you think about the future generation of clinical research professionals, what three "lessons learned" would you like to share?

A: Know what you know, and what you don't know—and feel OKAY about it. Early in my career, I thought I had to know everything and be good at it all. I was a perfectionist and very hard on myself. As I have grown in my career (and yes, I will admit it to you, gotten older), I recognized that one person can't have all of the experience in everything. I have to say how freeing this was for maintaining my self-esteem and credibility.

Commit to being a life-long learner in both technical abilities and interpersonal abilities. This may occur by reading, attending webinars, and so forth. Research the professional associations in your area and plan on attending their local meetings (e.g., ACRP, SoCRA, Project Management Institute, Society of Quality Assurance, American Society of Quality, Association of Quality, Regulatory Affairs Professional Society, National Speakers Association, Toastmasters), access the ACRP Global Conference presentations through the Online Conference Library (at a very nominal fee for those who do not attend), and search YouTube for free videos on useful topics (you would be amazed what is on YouTube!). In addition to these, when I identify someone I admire (in research or not), attend a great talk or presentation, or identify people who handle themselves superbly at work, I make it a point to observe them—their demeanor, speech tones, use of words, body posture, and body language—and I take note to import this into my personal style. All of these recommendations have contributed to my personal and professional development.

Self-report issues or errors caused by something you have done or witnessed others doing. In my 46-year career in healthcare and research, I have observed significant errors affecting patient safety—once by a resident physician who did not admit an error with a patient, and once with a sponsor organization. NO error in our industry is too small or trivial to not self-report. Find the opportunity to learn from the error, identify any risk with the error (subject safety? data reliability?), improve upon the situation, and move on. The subjects in our studies expect us to do our jobs well, and yet we are human, so issues/errors occasionally occur. Self-reporting our errors provides a vantage point to consider when placing the subjects first and rendering quality in our day-to-day jobs, with a focus on continuous improvement.

Q: Do you have any closing thoughts you would like to share?

A: Thank you for this opportunity to share my experiences. If you had told me in my 20s as a clinical nurse at JHH (visualize caring for sick patients, bed baths, bedpans, patient treatments, etc.) that I would be managing my own business, volunteering, collaborating, and working with teams of revered, talented, expert colleagues, I would have said, "Really?" The culmination of my experiences, and taking on a career path before my clinical research days that was "not a fit," guided and directed me to where I am today. The constants that aid in success are:

- know your passion
- work in your passion
- focus and commit to lifelong learning in many domains (not always technical)
- have a life outside your work

What worked for me was a systematic analysis of my "innate skills, aptitudes, and abilities" and matching my passion to those areas of clinical research.

- give back by volunteering in your community or elsewhere (find a cause you are passionate about)
- surround yourself with people who augment your skills or fill in your "gaps" (a team makes it all possible, rewarding, and FUN)
- recognize, compliment, and praise others (don't take it for granted that they feel appreciated and respected)

I owe a lot of these pearls of wisdom to my biggest fan and first and best mentor, my sister Penny. She passed away unexpectedly 20 years ago. What she taught me, I continue to reference and embody in who I am today, both in business and personally. Lastly, I have found great inspiration in a quote from Peter F. Drucker, an Austrian-born American management consultant, educator, and author (*New York Times* best seller), whose writings contributed to the philosophical and practical foundations of the modern business corporation:[2]

"Today knowledge has power. It controls access to opportunity and advancement."

I hope it inspires you, as much as it has inspired me.

Liz, thank you for sharing your own pearls of wisdom, insights, experiences, and practical advice; you live the life of a trainer and honor all of your mentors. Even within this interview, you are full of suggestions to help guide the path of future clinical research professionals.

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Impact of Clinical Study Regulatory Approval Delays in Brazil

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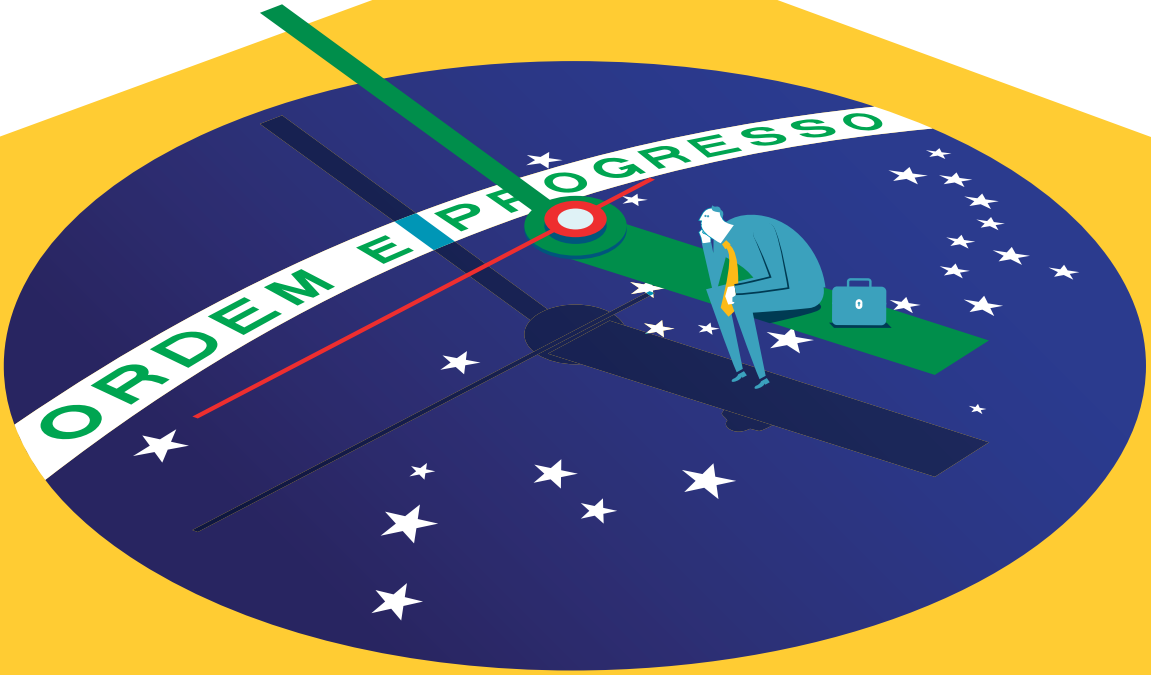
As the largest country in Latin America, Brazil boasts impressive socioeconomic indicators, including an estimated population of 200 million in 2012 (rank: 5th worldwide),[1] a Gross Domestic Product (GDP) in excess of 2 trillion USD (rank: 7th),[2] and annual pharmaceutical market sales of nearly 28.5 billion USD (rank: 6th).[3]

In addition to a favorable and stable economic environment, strong culture, and regulatory compliance to good clinical practices by trained investigators and staff, Brazil's well-structured research sites have been attracting international investments over the past decade. Some of these investments are reflected in terms of the growth of international clinical studies conducted in the country from 16 Phase II and III industry-sponsored studies in 2002 to 103 in 2012.[4]



Following the Process

The regulatory process for implementing a clinical study in Brazil requires evaluation and approval of the proposed research by two entities within the Ministry of Health: an ethical approval by CONEP (*Comissão Nacional de Ética em Pesquisa* – National Ethics Committee) and a logistical approval by ANVISA (*Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance). In fact, two ethics committees—an institutional ethics committee [IEC] at the local level and CONEP at the national level—approve the same documentation.

Considering multicenter studies, a coordinator site must be selected and the study protocol and related documents must first be approved by this site's local IEC, then forwarded to CONEP. Once granted final CONEP approval, all documentation must also be submitted to every single planned study site for obtaining approval from the local IECs.[5]

For ANVISA's logistics evaluation, the sponsor is responsible for providing a description of the study and related supplies (medication, lab kits, and equipment). After ANVISA approves the study, a license must be secured to start the supplies import process (see Figure 1 for a diagram of the study approval process in Brazil).

In many other countries, there is a single committee approval and, for instances where there is a national agency, it has the function of only supervising and supporting local ethics committees.[6]

Where to Go From Here?

Although a remarkable increase in the number of studies conducted in Brazil can be seen in recent years, initiating trials is a very challenging process, since timelines are unpredictable and considerably longer when compared to typical cases in other countries. Unfortunately, quite often international sponsors request the discontinuation of the approval process in Brazil once other countries have already finished their enrollment of patients.

However, there is hope for improvement: In January 2012, a new electronic submission process *(Plataforma Brasil)* was implemented in Brazil, intended to give greater security to the registration and monitoring of research. The rest of this paper aims to analyze Brazilian participation in international clinical trials, as well as to evaluate the impact of the regulatory process on performing clinical studies in Brazil.

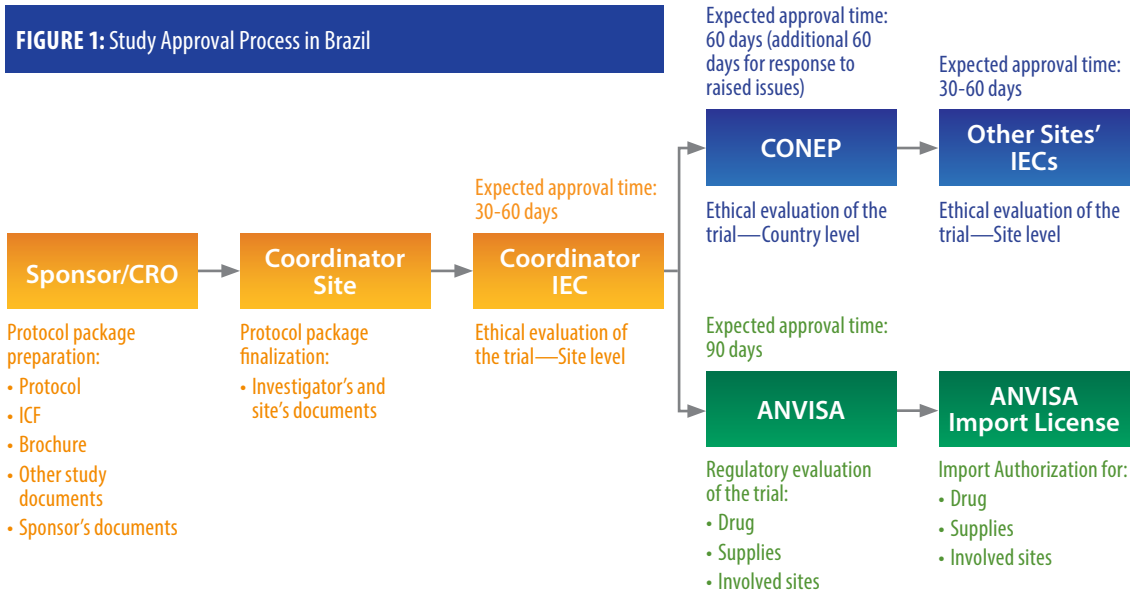
Material and Methods

Brazil in the Context of BRIC Countries and Latin America

For the purpose of comparing participation in clinical trials, a total of six countries were selected:

- Four BRIC countries: Brazil, Russia, India, and China were chosen due to the similarity in their stages of economic development; and
- Two Latin American countries: Argentina and Mexico were chosen due to the similarity in political and cultural aspects within the region.

FIGURE 1: Study Approval Process in Brazil



CRO: contract research organization; ICF: informed consent form; IEC: institutional ethics committee; CONEP: *Comissão Nacional de Ética em Pesquisa* – National Ethics Committee; ANVISA: *Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance.

A basic economic index based on GDP with last available data from 2012 and on population (from 2013) was used as a reference to economic development, and was obtained from publicly accessible websites (http://data.worldbank.org/data-catalog/GDP-ranking-table and http://worldpopulationreview.com). Details on numbers of studies were obtained from ClinicalTrials.gov.

ClinicalTrials.gov is a web-based registry maintained by the U.S. National Library of Medicine and updated by the sponsors or principal investigators of the clinical studies listed in its database. This registry includes general information about medical studies in human volunteers in 185 countries.[7] It was first made available to the public in February 2000, and its registration requirements were further expanded in 2007, under the Food and Drug Administration Amendment Act of 2007, Section 801. Data from 2007 onward were more reliable for this comparison.

The search comprised the allocation of industry-sponsored Phase II–III clinical studies to the six countries mentioned above in the calendar year of 2012 compared to the calendar year of 2007. No significant variations, either for increases or decreases, were noted in the years of 2008, 2009, 2010, or 2011 that could cause any bias to this analysis.

Overview of Regulatory Approval Process in Brazil

Forty-six industry-sponsored studies allocated to Brazil with available long-term submission data and started between June 2007 and June 2013 were selected for this analysis: 28 (61%) were successfully approved and 18 (39%) were discontinued during the process due to the delay in approval and conclusion of patient enrollment by other countries that were allocated to the same studies.

For the 28 approved studies, information about ethics (from the applicable IECs and CONEP) and National Agency (ANVISA) approval times has been collected. Also, data on the first patient screened in Brazil were compared to first patient screened in the overall study. Brazilian local timelines were also compared before and after *Plataforma Brasil*.

Statistical Analysis

Statistical analysis was performed for studies allocated to Brazil before and after *Plataforma Brasil* by an independent non-paired t-test of means. The level of statistical significance was set at $p < 0.05$.

TABLE 1: Comparison of Study Allocation in 2012 vs. 2007

Country	GDP (rank)*	Estimated Population (rank)**	Number of Studies***			Trial Density	
			2007	2012	2012 x 2007	2007	2012
Brazil	2,252,664 (7th)	200,674,130 (5th)	120	106	-11.7%	0.60	0.53
Russia	2,014,776 (8th)	142,572,794 (9th)	205	229	11.7%	1.44	1.61
India	1,841,717 (10th)	1,210,193,422 (2nd)	161	73	-54.7%	0.13	0.06
China	8,358,363 (2nd)	1,384,694,199 (1st)	90	136	51.1%	0.06	0.10
Mexico	1,177,956 (14th)	122,730,392 (11th)	134	136	1.5%	1.09	1.11
Argentina	470,533 (26th)	41,499,700 (32nd)	142	135	-4.9%	3.42	3.25

GDP: Gross Domestic Product.
* Data presented in millions of U.S. dollars for 2012, available at http://databank.worldbank.org/data/download/GDP.pdf
** Data estimated for 2013, except for India (2011), available at http://worldpopulationreview.com/countries/
*** Data from http://clinicaltrials.gov (Phase II–III and industry-sponsored), total of 3,292 studies (2007) and 2,777 studies (2012)

Results

Brazil in the Context of BRIC Countries and Latin America

According to data available at ClinicalTrials.gov, a total of 2,777 Phase II–III industry-sponsored studies were conducted worldwide in 2012, for a reduction of 15% compared to 2007 (n = 3,292). For BRIC countries, despite the fact that overall variation was almost null, there was a striking difference between the increases in Russia (11.7%) and China (51.1%) when compared to reductions in Brazil (-11.7%) and India (-54.7%). Argentina (135 studies) and Mexico (136 studies) have maintained their participation, conducting around 30% more clinical studies than Brazil in 2012 (see Table 1). In fact, Brazil has a significantly lower trial density (number of studies divided by estimated population in millions) during the same period.

Overview of Regulatory Approval Process in Brazil

Regulatory approval timeline data were considered only for the 28 approved studies. On average, it takes 46 days to obtain the local IEC's approval (range from seven to 248 days) in Brazil. There is a substantial increase in timelines when approvals at CONEP (average 175 days; range 62 to 362 days) and ANVISA (average 168 days; range nine to 328 days) are considered, adding a regulatory approval of at least six months.

Compared to other countries, this timeline forces Brazil to start recruiting patients on a first patient/first visit (FPFV) basis 11 months (328±120 days) later than other countries (see Table 2). All other evaluated countries were estimated to be ready for FPFV in less than 30 weeks after receiving documentation (internal data).

TABLE 2: Approval Timelines of Studies Successfully Implemented in Brazil

	Total	IEC	CONEP	ANVISA	FPFV
Average (days)	378	46	175	168	328
Median (days)	358	35	159	144	303
Standard Deviation (days)	96	46	83	87	120
Minimum–Maximum (days)	256–587	7–248	62–362	9–328	170–609

IEC: Institutional Ethics Committee; CONEP: *Comissão Nacional de Ética em Pesquisa* – National Ethics Committee; ANVISA: *Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance; FPFV: first patient/first visit.

TABLE 3: Approval Timelines for Canceled* Studies in Brazil

	Total	IEC	CONEP	ANVISA
Mean (days)	296	47	204	215
Median(days)	299	39	201	225
Standard Deviation (days)	88	46	55	91
Minimum–Maximum (days)	161–497	0–209	133–293	77–359

IEC: Institutional Ethics Committee; CONEP: *Comissão Nacional de Ética em Pesquisa* – National Ethics Committee; ANVISA: *Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance; FPFV: first patient/first visit.

* Canceled means study has been given up before approval by the required entities

For the 18 canceled studies (see Table 3), timelines are much longer and could not be correctly assessed. It took 10 months (296±88 days) from the first local IEC submission until the sponsor's final decision to give up the study in Brazil.

Based on the growth observed during the same period in BRIC countries (2007 vs. 2012; see Table 1), which are regarded as being in the same stage of economic development, Brazil could have conducted 40 more studies (106 actual vs. 146 projected) within the increment of studies allocated to China, Russia, and India (see Table 4).

Regulatory Approval Process after Plataforma Brasil

Twenty-eight initiated studies were compared regarding approval timelines before and after the *Plataforma Brasil* new submission process; 24 studies were submitted before its launch and four after. Regulatory timelines before and after *Plataforma Brasil* are shown in Table 5. There was a tendency for increasing regulatory timelines of 1.3 month (38 days) at CONEP (169 vs. 208 days; $p = 0.40$) and a significant increase of almost four months at ANVISA (151 vs. 266 days; $p = 0.01$), which means a total regulatory impact of 166 days (354 vs. 520; $p = 0.00045$), on average.

Discussion

According to the International Federation of Pharmaceutical Manufacturers & Associations, the introduction of a new drug is a long process that often takes from 10 to 15 years. From each five screened compounds from a total of 5,000 to 10,000 entering clinical trial phases, only one is approved.[8,9] In addition, it is estimated that only two out of 10 marketed drugs generate revenues that exceed research and development costs.[10] Therefore, pharmaceutical companies must have in place efficient mechanisms of managing this high-risk drug development process.[11]

TABLE 4: Number of Estimated Studies that Could be Conducted in Brazil Based on BRIC Countries and Latin American Data (2012 vs. 2007)

Region	Average # Studies	**Δ Brazil
BRIC	146 *	40
Latin America	136	30

* Brazil was not included in the calculation, only the average between Russia (229), China (136), and India (73) for BRIC; and Argentina (135) and Mexico (136) for Latin America.

** Δ Brazil was calculated based on the difference between the average number of studies performed in BRIC and Latin American countries, and the number of studies effectively conducted in Brazil (106) during the same period.

More specifically for the process of clinical trials, study allocation is an essential step, and ethics review of research is vital to protect the rights and safety of subjects.[5,12,13] However, in practice, the current process in Brazil is not only time consuming, it also deprives too much of the Brazilian population in general and too many researchers in particular from participating in innovative clinical trials.

As early as 2008, an independent report developed by the clinical research community had already stressed structural and operational problems that prevented Brazil from achieving good results in clinical research. At that time, some measures, like complete decentralization of the IEC-CONEP system for multicenter studies with foreign participation, adoption of a single system of questioning for a research project, and tacit approval as well as elimination of the requirement for presentation of foreign approval documents, were proposed to improve the system,[6] but none of them were implemented.

The Ministry of Health in Brazil requires a double ethical approval by the local IEC and CONEP for Phase I–III studies or for any clinical studies that have foreign co-participation. This is one of the steps that cause the most delays in the regulatory evaluation process. This legislation is not in harmony with other countries from Latin America and the world, which require only one step in ethical evaluation. Efforts are being directed to implement a change to the current situation of double ethical evaluation in Brazil.

The Brazilian studies mentioned in the present analysis covered different areas of treatment, but if we consider that the country starts recruiting patients on average 311 days after other countries, it means that many more patients could have participated in clinical studies performed in Brazil. In fact, Christie et al. has evaluated the impact of delays in approval process in oncologic studies in

TABLE 5: Comparison of Studies Initiated before (n = 24) and after (n = 4) *Plataforma Brasil*

	Total Timeline		IEC		CONEP		ANVISA	
	Before	After	Before	After	Before	After	Before	After
Mean (days)	354	520	46	46	169	208	151	266
Median (days)	361	523	35	41	173	208	139	293
Standard Deviation (days)	79	58	49	35	83	82	78	80
Minimum (days)	271	449	7	11	62	128	9	149
Maximum (days)	564	587	248	91	362	287	292	328

IEC: Institutional Ethics Committee; CONEP: *Comissão Nacional de Ética em Pesquisa* – National Ethics Committee; ANVISA: *Agência Nacional de Vigilância Sanitária* – National Agency of Health Surveillance.

Australia, and concluded that they have an effect on the survival of cancer patients. The survival rate from all types of cancer in Australia is improving at a rate of just more than 1% per year. A delay of two months in this improvement represents approximately 60 avoidable cancer deaths. Although not all trials save lives, each patient for whom entry into a trial is prevented because of these delays has therefore lost a significant opportunity to have access to state-of-the-art drugs and newer therapeutic approaches.[14]

In addition, 39% of studies were canceled due to the impractical timelines observed either at CONEP, ANVISA, or both, emphasizing the inefficiency of the country in terms of competitiveness in the clinical research environment. None of these studies was "purely" placebo-controlled. The sponsor had committed to provide assistance and study medication to patients on a post-trial basis, which adds inconsistent requirements to already unpredictable timelines, making for an increasingly challenging environment in which to conduct international industry-sponsored studies in Brazil. Nevertheless, in those studies for which Brazilian investigators obtained regulatory approvals in a timely manner, researchers delivered outstanding performances, enrolling a significant number of patients.[15–17]

Recent evaluation shows that there is still a gap, even after implementation of *Plataforma Brasil,* the new electronic submission tool; there was a significant increase in regulatory timelines, mainly at ANVISA. Furthermore, according to ABRACRO *(Associação Brasileira das Organizações Representativas de Pesquisa Clínica* – Brazilian Association of Contracted Research Organizations), of the 85 protocols recently submitted (January 2013 to March 2014) to CONEP and ANVISA, which would benefit around 4,971 patients and many clinical investigators, only 12 (14%) were already approved by both entities. Further, during the same period, CONEP was able to evaluate 30% more studies than ANVISA.[18] This recent analysis reflects an ongoing process of adaptation to the new electronic tool, which may improve over the time.

As a consequence, sponsor management teams are now accepting and committing only to participating in projects with a large number of patients and longer recruitment periods while planning studies in Brazil, rendering the country a noncompetitive environment in terms of clinical research scenarios. In fact, this impact can already be seen, based on the analysis of the number of studies that could potentially be conducted by the country when compared to the performance observed in some BRIC and Latin American countries.

Finally, there are some important points to be considered regarding how clinical research is conducted with and/or affects the people of Brazil:

- The results of trials conducted in high-income countries may not always be applicable to the Brazilian population.
- Local investigators must have the opportunity to contribute to the design of clinical trials that they are going to conduct.
- In addition to financial losses that certainly occur to the country, there is also a loss of "image," since Brazil is becoming an increasingly difficult country in which to work.
- The proposed changes already noted in 2008[6] still figure as the main contributors to promote a change in the current clinical research scenario in Brazil.
- Several actions from civil associations such as the National Investigator Society, patient-focused disease societies, and the Pharmaceutical Doctors Society, which recently created the Clinical Research Alliance Brazil, are important initiatives to expedite the regulatory process in the country.[6]

Conclusion

Brazil has a huge potential for conducting clinical trials; sponsor, investigators, and authorities should work together for developing an easy, efficient, and predictable approval process. Despite all the difficulties, Brazilian investigators are most often top recruiters of the trials they conduct. This regulatory environment must be improved; otherwise, it will not result in tangible patient, society, and medical benefits.

In addition to a favorable and stable economic environment, strong culture, and regulatory compliance to good clinical practices by trained investigators and staff, Brazil's well-structured research sites have been attracting international investments over the past decade.

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Although a remarkable increase in the number of studies conducted in Brazil can be seen in recent years, initiating trials is a very challenging process, since timelines are unpredictable and considerably longer when compared to typical cases in other countries.

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CLINICAL TRIALS IN JORDAN:

Current Status and Improvement Opportunities

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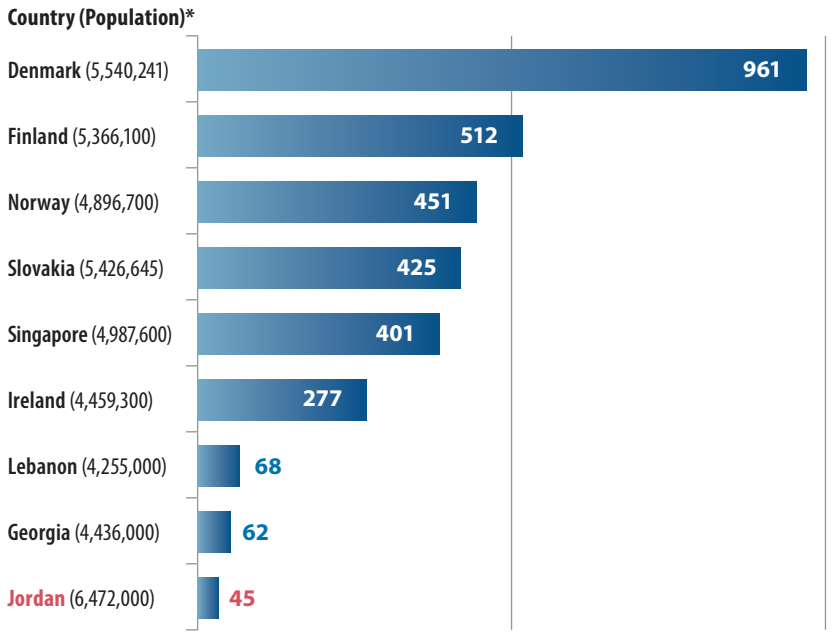
Performing research under conditions of robust methodology is key for the development of new drugs and medical devices. However, the conduct of clinical trials within countries in the Middle East and North Africa (MENA) is not yet optimal. Even though MENA populations represent 9% of the world population,[1] in 2012, MENA countries, excluding Israel, hosted only approximately 0.4% of global clinical trial sites and patients.[1]

In the mid-1990s, clinical trials started to gain recognition in Jordan, one of the MENA countries, with a very limited number and types of trials. A decade later, Jordan was recognized as one of the important research sites in the MENA area. Several contract research organizations (CROs) were established there in the early 2000s, focusing solely on bioequivalence and bioavailability studies.[2]

There are several reasons for the recognition Jordan has earned, including its highly qualified healthcare professionals and well-established and accredited healthcare organizations. It is a referral country, with regional healthcare centers receiving patients from all surrounding countries in the region as they seek advanced medical treatment. Further, the country features high bioethical standards, resources availability, and a supportive regulatory body. This environment fosters a heterogeneous patient population with various ethnic and cultural origins, which is ideal for clinical trials.

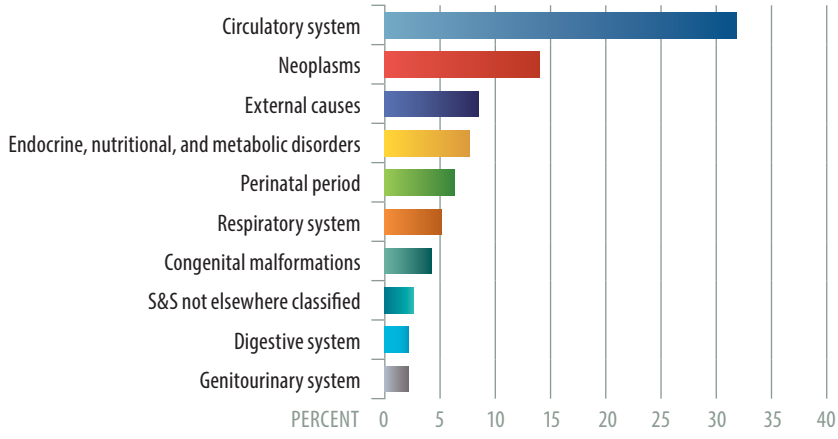
Concerning clinical trials, Jordanian law does not distinguish between the different kinds of pharmaceutical studies, even though there are clear definitions for therapeutic vs. nontherapeutic trials. This article reviews mainly Phase I to Phase IV clinical trials.

FIGURE 1: Number of Trials in Selected Countries



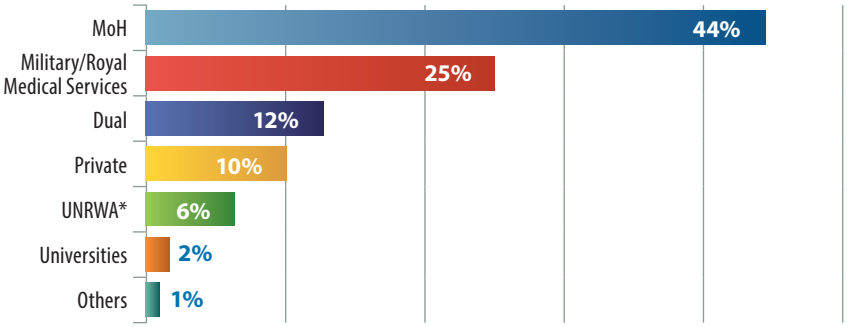
**World Atlas.com*

FIGURE 2: Top Ten Causes of Death for 2010 According to ICD-10



Source: MoH, Directorate of Information and Research, Mortality Data, Issue Dated May 1, 2011

FIGURE 3: Insurance Distribution 2010



**United Nations Relief and Works Agency for Palestine Refugees in the Near East.*
Source: High Health Council and Directorate of General Statistics, Medical Insurance and Payment, Issue Dated September 2011

FIGURE 4: Health Research Priorities 2009-2012

1	**Noncommunicable Diseases:** cardiovascular, cancers, injuries, endocrine, obesity, osteoporosis, and neuropsychiatric
2	**Maternal and Child Health:** prenatal and nutritional deficiencies
3	**Reproductive Health**
4	**Health Behavior:** smoking, dietary habits, drug abuse, etc.
5	**Health System and Health Policy**
6	**Environmental Health**
7	**Communicable Diseases:** hepatitis B and C, respiratory infections, diarrheal diseases, etc.
8	**Demographic Transitions**
9	**Oral Health**

DEMOGRAPHICS

The estimated population of Jordan at the end of 2012 was 6,388,000, with an annual growth rate of 2.2%. Approximately 60% of the Jordanian population are between 15 and 64 years old, and the life expectancy of the country's citizens is 73 years.[3]

Despite the fact that the Jordanian population is small, sponsors and clinical trial stakeholders recognize the research potential of Jordan. Figure 1 presents details on clinical trial activity and population in a selection of countries with a similar or smaller population than that of Jordan.

The most common cause of death in Jordan is circulatory disease, such as ischemic heart disease, cerebrovascular disease, hypertension, and heart failure. The top 10 causes of death in the country, according to the International Classification of Diseases (ICD-10) in 2010, are shown in Figure 2.[4]

The Jordanian health system is highly acclaimed, including primary and advanced healthcare services. Further, approximately 70% of the Jordanian population has healthcare insurance (Figure 3 demonstrates the distribution of insurance for the Jordan population).[3]

Circumstances related to the causes of death, management of the healthcare system, and availability of insurance in Jordan have had an impact in identifying research priorities. The Ministry of Health/Directorate of Information and Research has identified the "National Health Research Priorities 2009–2012," which has shown that noncommunicable diseases have the highest priority, while oral health has the lowest (see Figure 4).[4]

Although Arabic is Jordan's official language, all source documents are in English, including medical notes, progress notes, laboratory results, radiology reports, and medication prescriptions. English is the primary language of education for all healthcare professions, including medicine, dentistry, nursing, pharmacy and pharmacology, and rehabilitation sciences. However, patient materials such as questionnaires and consent forms should be in Arabic.

TYPE AND STATUS OF STUDIES

The number of clinical trials in the MENA region remains very low compared to the United States, Canada, Europe, and most of the Asian countries. However, Jordan is a leading country in the region in this field, especially in bioequivalence and bioavailability studies.[5] The approximate number of these studies submitted between 2005 and 2013 was 1,470 studies (for registered and unregistered products). Of these and the 135 Phase I–IV studies conducted between 2005 and 2013, only six were rejected, while the rest were approved or received at least conditional approval.[2]

The first registered clinical trial under the Jordan Food and Drug Administration (JFDA) was initiated in 2001. In 2010, there were 34 clinical trials: 19 Phase I and the rest Phase II to IV. In 2014, up to early October, there were 26 clinical trials submitted (four Phase IV and 22 Phase I to III).[2]

The main sources of clinical trials coming to Jordan are global pharmaceutical companies from Europe and the U.S., in addition to a few studies from U.S. biotechnology companies. Most of these studies were conducted in collaboration with regional or global CROs.[2]

To date, the most common phase of clinical studies conducted in Jordan is Phase III, followed by Phase IV. Although pediatric and medical device studies are permitted, there is no significant increase to the total from the number of studies conducted in these areas.[2] Figure 5 shows the number and type of submitted studies per year from 2005 to 2013, as well as the approved number of studies vs. rejected or conditionally approved studies. Figure 5 also shows the distribution of clinical trials according to therapeutic areas.[2]

REGULATORY

The highest governing body of all types of clinical trials in Jordan is the Ministry of Health (MoH)/ JFDA, which was established in 2003. By late 2004, the clinical studies division was initiated.

JFDA plays a very important role in the protection of the rights and safety of participants and in maintaining a high level of ethical standards through continuous visits, inspections, and monitoring of clinical sites and institutional review boards (IRBs). In addition, JFDA is responsible for training and maintaining an increased awareness of research among healthcare professionals and the public through educational meetings and conferences.

FIGURE 5A: Approved vs. Rejected Studies 2005-2013

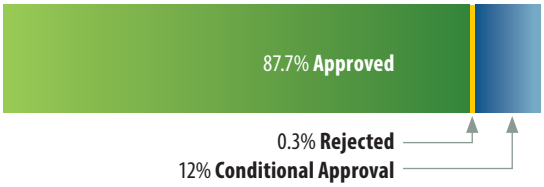


FIGURE 5B: Total Number of Studies from 2005 to September 2014

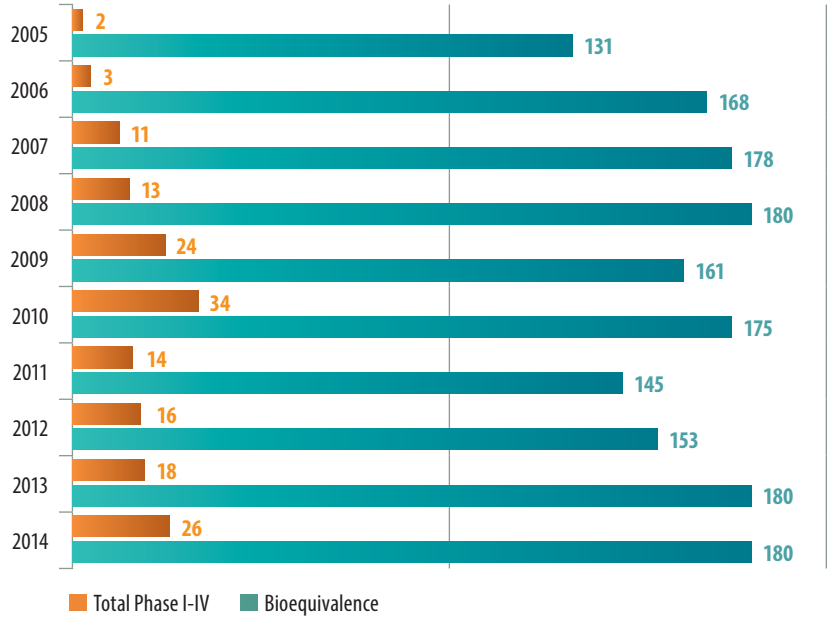
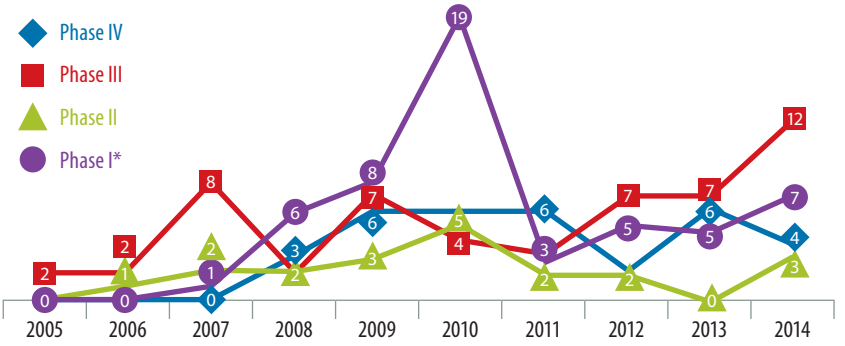


FIGURE 5C: Number of Phase I-IV Studies per Therapeutic Area 2005-2013



*Only one study in 2014 was first-in-humans; the rest were drug-drug interaction and pharmacokinetics.

FIGURE 5D: Number of Phase I-IV Studies per Therapeutic Area 2005-2013

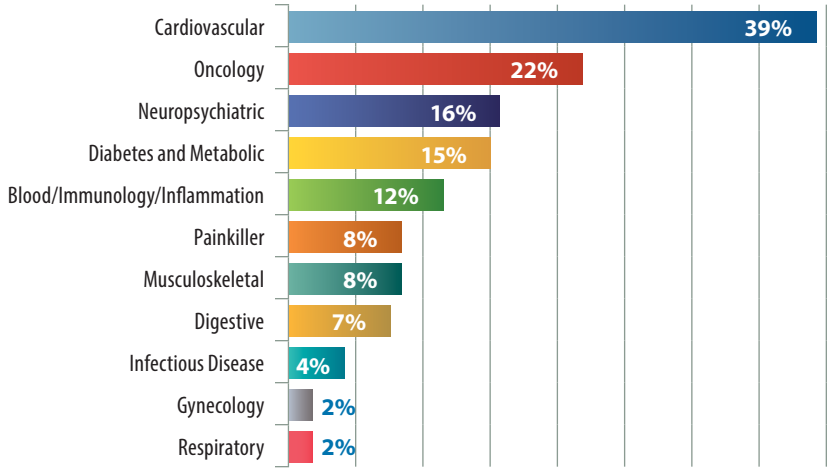
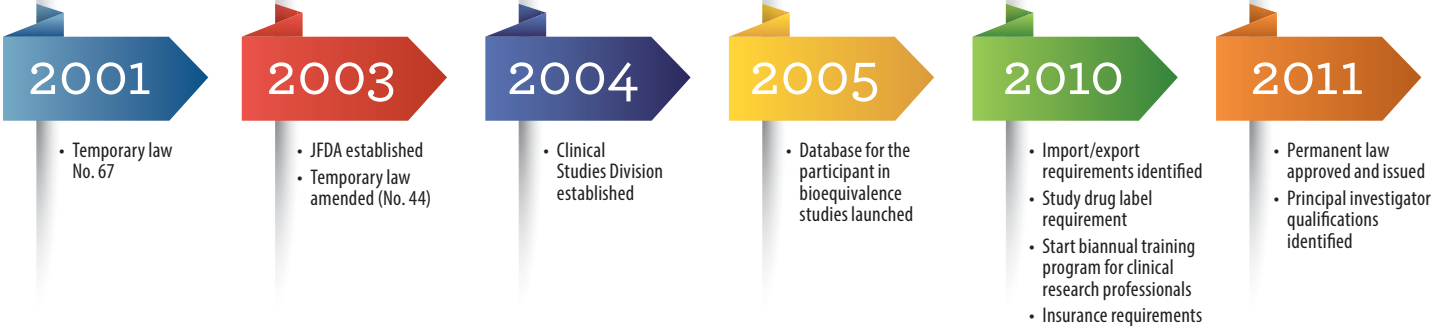


FIGURE 6: Significant Milestones in Clinical Trial Regulations in Jordan



The CSC has all the required powers to carry out its mission, especially since it was formed according to Jordanian law.

In 2004, the JFDA created the Clinical Studies Committee (CSC) to be responsible for reviewing and issuing approval or rejection for submitted studies. This committee is the highest authority for the initial decision on any new or ongoing study in human subjects.

The CSC has all the required powers to carry out its mission, especially since it was formed according to Jordanian law. Headed by the JFDA General Director, the committee includes the JFDA Director of Drug Directorate, the JFDA Head of the Clinical Studies Division, a pharmacist from the Drug Directorate, a clinician from the MoH, a clinician from the Physicians Labor Board, a member from the Royal Medical Services (military), and five representatives from academic and private institutions. The committee also has the right to consult external specialists as needed.

Healthcare research is now recognized and supported by governmental and private agencies, and Jordan is a leading country in clinical trials legislation in the Arab world. A temporary law issued in 2001 became permanent in early 2011; that law states that all clinical trials in Jordan should adhere to the Declaration of Helsinki as confirmed in Article 11. The law also specifies that one of the main duties for all local ethics committees is to ensure that the research team is able to conduct the study according to, and in adherence to, good clinical practice (GCP) guidelines (Article 8-a-2). Per Article 13-d, one of the main responsibilities of the CSC is to ensure that all licensed facilities for clinical trials adhere to GCP and good laboratory practice guidelines.[6]

However, the Jordanian law is currently written using wide and vague statements that are open to individual interpretations. Clearly written specific detailed guidelines or requirements would be of great benefit to all stakeholders. Since 2001, JFDA has issued more than 55 supportive memos, guidelines, and requirements to organize and improve the submission process, monitoring, and reporting. The most important examples of such memos and guidelines concern investigational drug labeling requirements and investigators' qualifications.

Figure 6 illustrates some important steps in clinical trials regulation. All these additions are made available in separate documents, but it is highly recommended that the documents be merged (including all clarifications), so that sponsors can consider all of the requirements together, rather than reviewing each individual memo from over the years.

SUBMISSION AND REVIEW

The expected time from full protocol package submission to final approval for conduct of a trial as estimated by JFDA is four to six weeks for Phase I–III studies, if there are no comments or additional requirements requested.[7] Otherwise, the approval time will vary based on the nature of the comments or requirements as well as on the sponsor's feedback. Next, the sponsor seeks approval from an IRB/ethics committee, based on any new requirements and with a commitment of adherence to them by the principal investigator and the sponsor. However, if the sponsor does not reply to the board's/committee's feedback regarding further changes that may be requested within six months, the application will be considered withdrawn.

One of the main issues for clinical studies in Jordan is the time the studies take to get approved; this has a negative impact on patient recruitment and study progress, and means that any eventual approval of a new drug or device is delayed. Therefore, the current submission procedures should be reviewed and more time-efficient strategies developed.

One issue of timeliness is that, currently, JFDA uses the sequential submission system as described where and does not accept parallel submission at the same time as IRB/ethics committee submission. Electronic submission is definitely a good approach for improving the submission process, yet all submissions must be delivered by hand to the JFDA at this time. The use of electronic submissions will save up to two to three weeks, with study documents reaching CSC members directly and with external reviewers facing no need to wait for the next meeting to receive materials for consideration.

JFDA plays a very important role in the protection of the rights and safety of participants and in maintaining a high level of ethical standards through continuous visits, inspections, and monitoring of clinical sites and institutional review boards.

The sponsor can submit all documents in English, except those for the patient (informed consent form, information sheet, patient's cards, questionnaires, diary cards, etc.), which should be in Arabic.

CLINICAL SITES AND IRBS

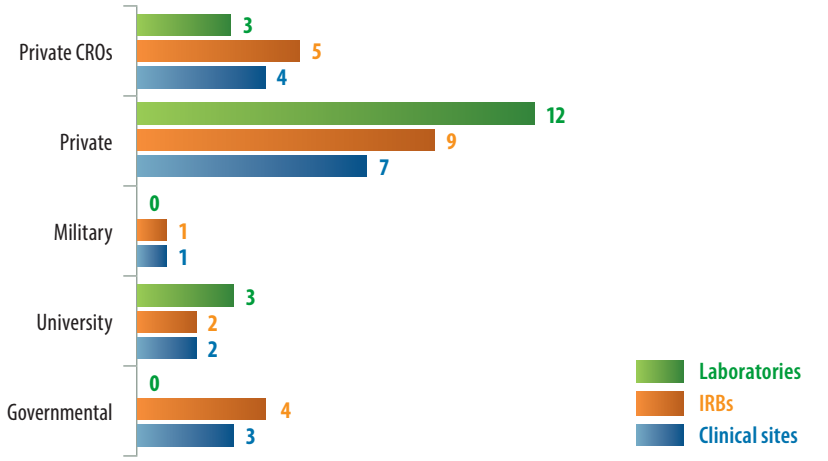
According to Jordanian law, clinical trials can be conducted only at licensed sites; the same process applies to all other involved facilities, including IRBs/ethics committees, safety labs, and analytical labs.

As of 2012, Jordan had 106 hospitals with a total capacity 12,106 beds.[3] These hospitals can be divided into four main categories: MoH hospitals, university hospitals, military hospitals (Royal Medical Services), and private hospitals. Most of the private, military, and university hospitals are accredited by one or more of the local or international accreditation bodies; they also have the most recent diagnostic and treatment equipment, use the Internet, and have no difficulties using electronic case report forms. In addition, these hospitals have local laboratories and/or research units to facilitate lab samples processing as well as shipping to central labs if needed. However, less than 20% of Jordanian hospitals are licensed as clinical trials sites (see Figure 7).[8]

Governmental and private hospitals need to make greater efforts to become involved in clinical studies. Currently, only three of 31 MoH hospitals are licensed for clinical trials; their physicians are interested in being involved in trials, but many issues—such as site facilities, medical documentation, and lack of experience and encouragement by top management—need to be resolved in collaboration with the MoH, sponsors, and regulators.

The military hospitals are well established and have an advanced documentation system for use in clinical trials. However, the number of clinical trials conducted in these hospitals is very low, due to the long time required to get IRB/ethics committee approval and contract negotiation. The top management in such settings needs to encourage greater interest and to establish research activity benchmarks against similar institutions.

FIGURE 7: Number of Licensed Facilities as of August 2014



For private sites as well, sponsors and investigators should clarify to patients the benefits of clinical trials, regardless of where they are treated, and healthcare workers should get more training and experience in clinical trials. Of the 18 licensed hospitals, only four have dedicated research units managing trials and providing the required logistic support to investigators.

Jordan does not use a central ethics committee; only IRBs/ethics committees based within individual institutions are used. Each licensed clinical site must have such a body, which should be approved by the JFDA. According to Jordanian law, the board/committee should consist of at least five members from both sexes with sufficient experience and competency.

An IRB/ethics committee is required to include at least one legal advisor in addition to a representative from the local community.[6] Board/committee membership is valid only for two renewable years.[6] Figure 7 shows the number of approved IRBs/ethics committees in Jordan.

CONCLUSION

Clinical trials are growing in the MENA region, and Jordan is a leading country in this area. Conducting a clinical trial in Jordan is protected by the government via the Clinical Studies Law and monitored by IRBs/ethics committees. The healthcare systems of the country are ready to be more involved in clinical trials.

All stakeholders must be willing to participate in clinical research, to provide more training and educational programs, and to develop more creative solutions for facilitating and expediting protocol submission, review, and monitoring, such as electronic submission, detailed guidelines for all trial steps, and benchmarking. Also, governmental hospitals require greater research awareness, training sessions, and improved support in terms of facilities, systems, and guidance.

Acknowledgment

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Margo Michaels, MPH

Starting the Discussion: 13 Simple Messages to Explain Treatment Trials

This new regular column focuses on challenges in recruitment, accrual, and retention for all types of clinical research trials.

When we talk about clinical trials with members of the public, people who are inquiring, or potential study participants, it's often difficult to determine exactly how much information is appropriate to provide, and at what stage. With only 12% of the U.S. population having proficient health literacy skills,[1] we must titrate the information we provide and use terms likely to encourage conversation or discussion. Remember that the purpose of such conversations is to generate continuing inquiry about the role and value of clinical trials in general, as part of a broader public and patient education process.

This first installment of this column looks at 13 simple messages to enable a productive discussion with patients to "prime" them for potential research opportunities in the future. The next column will examine ways to extend the general discussion to more specific messages that can be used before and during the formal informed consent process.

Although the following messages may seem easy to use, practicing them with a colleague would be wise before using them in a live setting.

1. Always start by asking, "What do you know about clinical trials or research studies?"
2. People often participate in a clinical trial, or research study, intended to find new ways to prevent, diagnose, or treat conditions like cancers, heart irregularities, allergies, genetic disorders, and much more. We may have treatments that work (well) today, but we are always trying to find treatments that work better for patients. The only way to find better treatments is through what we learn from patients participating in clinical trials.
3. There are two (three) ways we can treat (your condition) today:
   a. **Standard care**—the treatment that is accepted by medical experts as the best available
   b. **Receiving treatment within a clinical trial or research study**
   c. **Off-label use**—when a drug is used for a purpose that is different from that for which it was originally approved
4. Thousands of people participate in clinical trials every year. At our facility…(X number of trials are ongoing, or X number of patients are actively participating in clinical trials).
5. We want to make sure everyone learns about all the options for treating his or her disease, including receiving treatment within a clinical trial or research study.
6. Everyone taking part in a trial receives careful medical attention.

What is Health Literacy?

Health literacy—the ability to obtain, process, and understand basic health information and services to make appropriate health decisions—is an essential component to consider in the conduct of clinical research discussions.

Limited health literacy is not a disease that makes itself easily visible. In fact, you can't tell by looking; health literacy depends on the context. Even people with strong literacy skills can face health literacy challenges if:

- They are not familiar with medical terms or how their bodies work.
- They have to interpret numbers or risks to make a healthcare decision.
- They are diagnosed with a serious illness and are scared or confused.
- They have complex conditions that require complicated self-care.

Clinical research professionals may be surprised to learn the following facts[1]:

- Only **12%** of U.S. adults have proficient health literacy, such as that required to comprehend a standard informed consent form.
- More than **one-third of U.S. adults (77 million people)** would have difficulty with common health tasks, such as following directions on a prescription drug label or adhering to a childhood immunization schedule using a standard chart.
- Limited health literacy affects adults in all racial and ethnic groups. The proportion of adults with basic or below basic health literacy ranges from **28%** of white adults to **65%** of Hispanic adults.
- Although **half** of adults without a high school education had below basic health literacy skills, even high school and college graduates can have limited health literacy.
- Compared to privately insured adults, both publicly insured and uninsured adults had lower health literacy skills.

Excerpted from www.health.gov/communication/literacy/issuebrief/

7. No one receives a placebo (sugar pill/fake medicine) instead of appropriate treatment. (The word "appropriate" is intentionally used so that this sentence does not erroneously suggest placebos are not used in treatment trials.)

8. Participating in a clinical trial is not free, and all costs are not always covered by insurance.

9. Participating in a clinical trial is a personal choice:

- No one can be a part of study without giving the research team his or her explicit permission.
- Trials are not for everyone. There are rules about who can join each study.

10. There are laws to protect the safety of people participating in research.

All 10 sentences above are appropriate for general audiences. The following points would be important to make *directly* to a potential participant.

11. People who participate in trials do not get to choose the treatment that they want. Neither do the doctors. If you choose to participate in a study, you would receive (choose one):

a. Either the most accepted treatment for (the condition at hand) or a new treatment that doctors hope will be better. We don't yet know if it is better than what is now used to treat your condition, but we do know the new treatment is safe and effective from previous studies.

- The groups are assigned by a computer, and no one, not even your doctor, can choose which group you will be placed into (in the case of a randomized Phase III trial).

b. A treatment that has already been shown to be safe in humans. We don't yet know how effective it is for your disease (in the case of a Phase II trial).

c. A treatment that has already shown to be safe and effective in animals. We don't yet know if it is safe or effective for humans (in the case of a Phase I trial).

➢ ***We never use terms such as randomization, "flip of a coin," or stratification.***

12. If you decide to participate in a trial:

a. You can drop out at any time, and for any reason.

b. We are required to watch for any problems you may have. If you aren't doing well while you're on a study, we would not let you continue in that study.

13. As you consider whether you want to participate in a trial, you have the right to ask all the questions you need to help you make a decision. Part of my job is to help you answer them!

Stay tuned for the next installment of this column, which will provide simple ways to explain complicated concepts in clinical trials before and during the consent process.

For more information on topics related to this column, please visit the ACRP Clinical Trials Recruitment Interest Group online at www.acrpnet.org/Interest-Groups/Clinical-Trials-Recruitment-.aspx.

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Brent Ibata, PhD, JD, MPH, RAC, CCRC

Investigator-Initiated Clinical Investigations and Sponsor-Investigator Obligations

An investigator assumes the responsibilities and obligations of a sponsor when s/he initiates a clinical investigation using a drug or device subject to premarket submission to the U.S. Food and Drug Administration (FDA) under either section 505(i) for an Investigational New Drug (IND) or section 520(g) for an Investigational Device Exemption (IDE) as defined by the Federal Food, Drug, and Cosmetic Act (FD&C Act).

A *sponsor-investigator* is an "individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed"[1] for a drug study. Further, this person is an "individual who both initiates and conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used."[2] The regulatory obligations of a sponsor-investigator include those of a sponsor[3] as well as those of an investigator.[4]

The first determination that a physician must make when contemplating the intended use of a drug or device for an unapproved indication is whether the proposed use is a "clinical investigation" within the meaning of 21 CFR Part 50 (in the *Code of Federal Regulations*) or "research" within the meaning of 45 CFR Part 46 and therefore subject to informed consent requirements under 21 CFR Part 50 Subpart B and institutional review board (IRB) review under 21 CFR Part 56.

Clinical Investigations and Research Determination

A "clinical investigation" is defined at 21 CFR 50.3(c) as follows:[5]

> Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) [IND] or 520(g) [IDE] of the act, or is not subject to requirements for prior submission to the [FDA] under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the [FDA] as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

"Research" is defined at 45 CFR 46.102(d):[6]

> Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes.

Except as provided in 21 CFR 56.104 and 56.105, all clinical investigations that must be submitted to the FDA must be reviewed and approved by an IRB and remain subject to IRB continuing review.[7] Even if an investigator-initiated study is not a "clinical investigation" subject to FDA oversight, it may still be "research" subject to IRB oversight.

Narrow categories of research are exempt from the U.S. Department of Health and Human Services Policy for Protection of Human Research Subjects at 45 CFR 46.101, including:

- Research involving normal educational practices (45 CFR 46.101(b)(1));
- Narrow types of research involving the use of educational tests (45 CFR 46.101(b)(3)) and (b)(4);
- Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens (if publicly available or anonymized) (45 CFR 46.101(b)(4));
- Narrow types of federally sponsored research and demonstration projects (45 CFR 46.101(b)(5)); and
- Taste and food quality evaluation and consumer acceptance studies (45 CFR 46.101(b)(6)).

In its Guidance for IRBs, Clinical Investigators, and Sponsors,[8] the FDA advises that:

> FDA regulations require sponsors and sponsor-investigators (of individual investigator-initiated studies) to determine whether an IND is required for a particular study... For studies involving an investigational device, the sponsor is responsible for determining

If you have a research compliance issue you would like covered in this column, please send an e-mail to the author at **ibataba@gmail.com**.

whether submission of an IDE application to FDA is required before a study may proceed. The IDE regulations (21 CFR 812) describe three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies. SR device studies must have an IDE application approved by FDA and have IRB approval before they proceed, and they must follow all of the IDE requirements. NSR device studies must follow the abbreviated IDE requirements at 21 CFR 812.2(b), including informed consent and IRB review, and do not require submission of an IDE application to FDA.

Therefore, if an investigator-initiated study is subject to the submission requirements for an IND or IDE, the investigator assumes several sponsor responsibilities, including the obligation to:

- maintain specific records (21 CFR 312.57 and 21 CFR 812.140);
- prepare and submit reports (21 CFR 312.33, 21 CFR 312.56, 21 CFR 312.64, and 21 CFR 812.150);
- ensure proper monitoring (21 CFR 312.50 and 21 CFR 812.40); and
- ensure that an IRB that complies with 21 CFR Part 56 reviews and approves of the proposed clinical study (21 CFR 312.66 and 21 CFR 812.40).

Even if the investigator-initiated study is exempt from the IND requirements or the IDE regulations, the FDA IND/IDE Guidance notes that the study must still comply with 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review).[8]

Research Involving Lawfully Marketed Drugs or Devices

In its "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices–Information Sheet,[9] the FDA advises:

> Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an [IND], [IDE], or review by an [IRB]. However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required.

For drugs, it is fairly clear whether the drug is legally marketed since drugs can be searched by active ingredient or proprietary name at www.fda.gov. For devices, this can be more difficult since the distinction between a medical device and a nonmedical device will turn on the "intended use" of the device.[10] A "device", within the meaning of the FD&C Act, is "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory" that is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals."[11]

If a new device has not been classified by the FDA, it is automatically classified as a class III device requiring an IDE and premarket authorization by operation of section 513(f)(1) of the FD&C Act.[12] The FDA's Center for Devices and Radiological Health has a product classification database that lists all medical devices, product codes, and associated classifications for devices lawfully marketed in the United States.

Conclusion

If a drug or device is not lawfully marketed in the U.S., it may be used as part of an investigator-initiated clinical investigation only if the investigator has obtained an IND, IDE, or an IRB has affirmed an NSR determination.[11] The investigational use of a drug or device as part of a "clinical investigation" without an IND or IDE is prohibited by section 301 of the FD&C Act, which subjects the drug or device to seizure under section 304 and the investigator to penalties under section 303. An investigator that intends to initiate a clinical investigation for an unapproved drug or device or an "off-label" use of an approved drug or device assumes the responsibilities, obligations, and risks of a "sponsor-investigator," the most important of which is assuring IRB review and obtaining adequate informed consent.

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2. 21 CFR 812.3(o). *See also* ICH E6 1.54 and 21 CFR 50.3 (f).
3. 21 CFR Part 312 Subpart D and 21 CFR Part 812 Subpart C.
4. 21 CFR Part 312 Subpart D and 21 CFR Part 812 Subpart E.
5. *See also* 21 CFR 56.102(c).
6. 45 CFR 46.102(d).
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NOTE: Vol. 28, Issue 1 (February 2014) was the last issue of *The Monitor.* Effective with Vol. 28, Issue 2 (April 2014), the journal was renamed *Clinical Researcher.*

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Founded in the year 2000, **FXM Research** is a privately owned and operated Clinical Research Site that conducts phase II, III, and IV clinical research trials specializing in Dermatology. Throughout the years, our ability to deliver aggressive, time bound enrollment goals, while providing trustworthy data to Pharmaceutical companies and CROs, has earned **FXM Research** a great deal of notoriety and fame within the Dermatology research industry.

Today, FXM Research's success is widely regarded throughout our four operating branches: **FXM Research Corp.**, based in Miami, Florida and home of our headquarters, **FXM Research Miramar**, located in the city of Miramar, Florida and **FXM Research International**, including two branches in Belize City, Central America.

OUR MISSION

At the core of our business and operating systems, **FXM Research** mission is to support pharmaceutical companies and CROs with introducing new and approved FDA medications successfully into the marketplace. We perform this efficiently and effectively by providing the highest quality service in a timely fashion and at the lowest possible cost.

- We specialize in conducting phase II, III, and IV Dermatology Clinical Trials.
- Our primary concerns are subject safety and adherence to the protocol.
- Turnover time for Regulatory Documents, budgets, and contracts is usually 24 to 48 hours.

OUR SUCCESS

- We offer experienced, trained, and bilingual personnel (English and Spanish), who interact with our subjects, sponsors, and CROs as a cohesive team.
- Our Principal Investigators are Board Certified Dermatologists and Certified Clinical Research Investigators with many years of extensive experience. They are located onsite and are available full-time.
- Most subjects are recruited from the office of our PI's private practice, and/or FXM Research's extensive clinical database. We draw heavily from a Spanish speaking population, a group often under-represented in clinical trials. We also have continuing extensive experience with a pediatric population.
- We do whatever is necessary to accommodate our subjects' school and/or work schedule, which maximizes compliance and retention.
- We are confident that we can surpass sponsors expectations relating to cost, subject enrollment/retention, and the quality of our work.

TO CONTACT US

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Join us for an upcoming online information session.
Wednesday, December 17, 12–1 pm
RSVP: grahamschool.uchicago.edu/clinicaltrials1217