ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

April 12, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5360 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket No. FDA–2015–N–3579: **Using Technologies and Innovative Methods to Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs; Establishment of a Public Docket**

Dear Sir or Madam:

ACRO would like to thank FDA for issuing the public docket to solicit input from stakeholders on the scope and direction of the use of technologies and innovative methods in the conduct of clinical investigations. Founded in 2002, ACRO represents the world's leading clinical research organizations (CROs), which provide specialized services integral to the development of drugs, biologics and medical devices.

- ACRO's mission is to advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.
- Each year, ACRO members conduct more than 9,000 clinical trials in 140 countries involving nearly two million research participants.
- In 2015, CRO industry revenue was estimated at $25.6 billion; that amount is expected to reach $27.8 billion in 2016.
- ACRO member companies employ approximately 110,000 people worldwide.

ACRO is a leading voice for safe and ethical clinical trials, working with stakeholders globally to promote a better and more efficient clinical trial process. We are dedicated to bringing efficiency, innovation and value to the clinical research process and to highlighting the important contribution CROs make as partners in the development of new medicines and new treatments that benefit millions of patients worldwide.

Given the degree to which ACRO members have visibility into the worldwide clinical trial process, ACRO developed this document to summarize our members' thoughts on how technology could greatly benefit the drug development process. Our topline recommendations include:

- Issue a public statement that the use of new technologies is encouraged in clinical trial conduct.
- Create a task force to work with Sponsors, CROs, patient groups and technology providers and health care providers on this path to learn first-hand the barriers and benefits

- Plan to adjust current guidance documents to allow for use of these technologies, as many guidance documents were written for a paper process, not technology-driven solutions.
- Adjust audit processes to take into account uses of new technologies, including more automation of the process and advanced training of auditors so they understand and adapt to the use of new technologies.

The FDA needs to provide clear guidance in terms of how to proceed related to security and monitoring requirements related to these new technologies. The FDA needs to be willing to share the progress being made in the industry, and provide feedback on the use of new technologies and inspection results. The FDA could take more of a leadership role in developing and enforcing data standards.

For regulated endpoints, endorsement and acceptance by the FDA is essential. Subject outcomes are often considered as a primary outcome, yet collecting this information may depend on the use of older methods that have been historically accepted by regulators. A major validation effort is needed to bring new developments to the point where they can be used for clinical trials. If the FDA is able to streamline the process – perhaps through a standardized acceptance procedure, or use of third party validation services – the adoption of new and innovative technology could be accelerated.

With the help of the FDA, more prescriptive guidance could be provided and working groups could be established to identify and address issues and implement standards. The driving of standards of data through these working groups would reduce variability and raise quality particularly by the time we reach testing phases of a solution.

Similar to the agency's risk-based monitoring (RBM) guidance, a position from the FDA could be vital in influencing our industry. In this context, clarifications around technology standards, source data and inspection requirements would be critically important.

In-silico clinical studies are increasingly being accepted as supporting evidence toward market authorization, decreasing the need for costly in-vivo studies. However, the predictive value of the models underpinning in-silico clinical studies is directly related to the quality and consistency of data used to generate and test these models. While Electronic Health Record (EHR) data is predominantly used today, usage of standardized clinical trial data, comparable across studies, would support building an increasing number of high quality predictive models; some of these models could be made publically available after testing and validation across the industry and would allow companies to avoid collecting new data that have been collected already in previous trials by other companies.

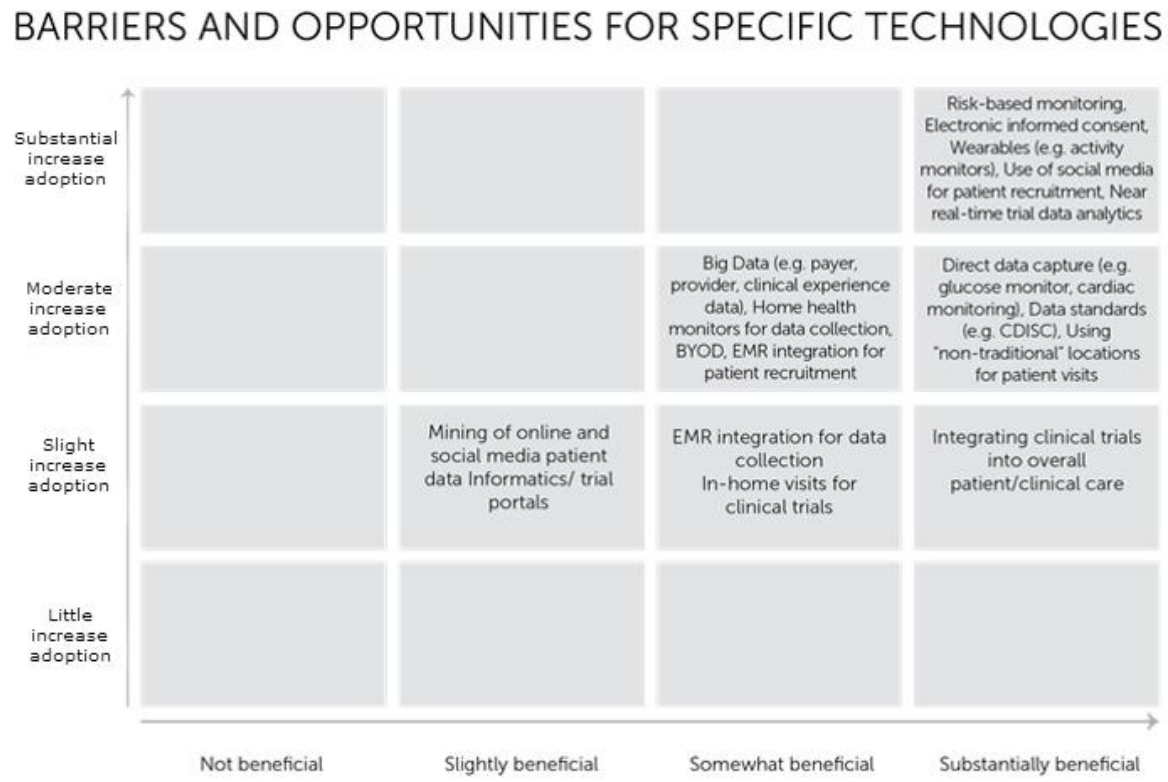
ACRO thanks its member companies for their time and attention in providing their thoughts and experiences on this important FDA response.

Barriers and opportunities for specific technologies

ACRO asked our members to rate several emerging technology applications on both the beneficial value and the adoption rate over the next 2-5 years.

“Looking out over the next 2-5 years, how **beneficial** will the following technologies be to the conduct of clinical trials?”

“Looking out over the next 2-5 years, what will the **adoption** trends look like for each of the following technologies used in the conduct of clinical trials?”



In short, ACRO members believe the majority of technologies listed above can be “substantially beneficial” to the conduct of clinical trials over the next several years. The technologies that ACRO members believe will provide the most benefit and will be most readily adopted in the coming years include: risk-based monitoring, electronic informed consent, wearables (e.g. activity monitors), the use of social media for patient recruitment, and near real-time trial data analytics.

As such, ACRO suggests the FDA focus its resources on providing guidance on those technologies that are most beneficial and most likely to be widely adopted.

In general, ACRO requests that the FDA take every possible opportunity to encourage adoption of new clinical trials technologies, including through public statements, guidance documents, position statements and regulations, as appropriate.

Specifically, in regard to high adoption/high benefit technologies:

Risk-based monitoring – The FDA (and EMA) has issued guidance on RBM and the CRO industry, with its sponsor partners, is leading the way on implementation. ACRO has been actively engaged with TransCelerate Biopharma on its RBM project. Additionally, we are in process of surveying our members to determine the most appropriate metrics.

eConsent – The FDA provided valuable guidance on eConsent in March 2015. As with RBM, ACRO is working with TransCelerate on a project around this topic and several of our members are innovating in the space. As technologies evolve, as patients become more comfortable and as IRBs and investigators adopt eConsent, there will be a need for ongoing guidance.

Wearables – Wearables represent a huge opportunity to make clinical trials more efficient, more convenient for participants and to gather additional data. At present, however, there lacks guidance on: data capture; data security and privacy; data standards and quality; data integration; and data analysis. The FDA could be very helpful in helping to drive adoption of wearable technologies in clinical trials by providing measured guidance. A delicate regulatory balance must be achieved, however, so that adoption is encouraged and technologies, such as apps, do not become overregulated.

Social media for patient recruitment – The FDA has been largely absent in addressing issues around industry's the use of social media, especially in the area of patient recruitment. As the agency is well aware, patient recruitment is a major hurdle for clinical trials and social media is proving to be an efficient, effective and direct way to recruit patients outside, or complementary to, the normal channel of investigators. ACRO suggests the FDA convene stakeholders to provide input into a guidance or "best practices" document so this powerful recruitment tactic can be deployed to its maximum potential without fear of regulatory reprisal.

Real-time trial data analytics – ACRO's members are leading the innovation in this area, either through direct investments in proprietary systems and/or the implementation of best-of-breed third-party technologies. These systems facilitate RBM and provide many other benefits to sponsors and CROs during the clinical trial process. While there are tremendous opportunities here to vastly increase the amount of data gathered and improve the timeliness of gathering data, a number of issues remain problematic concerning data capture, privacy, security, integration, storage and analysis.

Our detailed comments on these and other topics follows.

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Themes from ACRO members

Many of our members provided ACRO with detailed descriptions and examples of how the FDA-outlined technologies and clinical trial activities could be used to improve the drug development process. Several themes emerged from their commentary and are summarized below.

1. The biopharmaceutical industry is, given its heavily regulated nature, generally risk-averse to trying/adopting new technology and/or processes.
2. There is a lack of technology standards from which to develop new/interoperable technology products and services.
3. We are in a time of rapidly changing technology with new apps and wearable devices hitting the market on an almost daily basis. This makes data capture, integration and quality assurance challenging.
4. The lack of FDA regulatory guidance is hindering adoption of new clinical trial technologies.
5. Data security issues need to be addressed.
6. Data integration hurdles are currently quite high.
7. Change management is currently, and will continue to be, a necessary skill set to have before widespread adoption of new technology and processes are adopted. Technology is changing faster than the industry can change to take advantage of it.
8. The continued improvement in access to near-real time clinical trial data will open up possibilities that could dramatically improve patient safety and improve trial efficiencies.

After leading the industry's sometimes slow implementation of electronic data capture (EDC) and the continued sluggish adoption of electronic patient reported outcomes (ePRO) technologies that have the power to reduce paper data capture in clinical trials, ACRO members are eager to embrace new technologies to help improve clinical trial efficiencies. Our members would like to work in concert with the FDA to ensure we have learned from the past and the industry can accelerate the pace of change in the future with full support from the regulator. This effort will not be easy and the FDA must show a willingness to accept new practices or we will again face slow adoption or promising new technologies.

As the world moves from the fairly controllable and stable realm of enterprise-based technology applications, such as EDC and Clinical Trial Management Systems (CTMS) applications, to the emergence of personalized or individual-based technology, this has the power to unlock powerful data streams if it can be leveraged properly and the industry is willing to adopt them. ACRO members are looking to FDA to provide the foundation (e.g. guidance, standards, dialog) to help bring drive adoption of new technologies and capabilities to the clinical trial process.

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1. The biopharmaceutical industry is, given its heavily regulated nature, generally risk-averse to trying/adopting new technologies and/or processes.

Supporting material/discussions

ACRO members would like to see FDA issue statements/guidance that use the word "encourage" or something similar to signal to the industry that the use of a new technology/process is, in fact, encouraged. Create a task force to work with CROs, sponsors, investigators, patients and technology providers to learn first-hand the barriers and benefits of particular technologies in a real-world setting. Plan to adjust current guidance to allow for use of these technologies as many of the guidance documents were written for a paper process, not technology-enabled clinical trials.

Themes from ACRO members

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2. There is a lack of technology standards from which to develop new/interoperable technology products and services.

Supporting material/discussions

ACRO members would like to see FDA take a leadership role in promoting and encouraging data standards. A major validation effort is needed to bring new developments to the point where they can be used for clinical trials. If FDA is able to streamline the process – perhaps through a standardized acceptance procedure, or use of third party validation services – the adoption of new and innovative technologies could be accelerated. With the help of FDA, more specific guidance could be provided and working groups could be established to identify the best current standards (e.g. CDISC) or develop new standards and determine the best ways to implement them across the industry. The driving of data standards through these working groups would reduce variability and raise quality particularly by the time we reach testing phases of a solution.

Themes from ACRO members

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3. We are in a time of rapidly changing technology with new apps and wearable devices hitting the market on an almost daily basis.

Supporting material/discussions

The use of wearable sensors is not new in clinical trials. CROs and sponsors have a history of the provision and management of devices as well as the management and interpretation of their data in clinical trials. Such devices include, for example, spirometers and glucose meters provided to subjects for intermittent use as scheduled by the study protocol. These devices historically stored data that could be retrieved by connection to a PC during a clinical site visit. More recently, the advent of internet and telecommunications connected devices has enabled the real-time collection and reporting of this data, sometimes in combination with ePRO assessment. The ability to collect data on trial participants between clinic visits provides important additional information about the effects of treatment and can supplement and sometimes replace data recorded during visits to study sites. In addition, real-time access to these data enhances both subject safety and the monitoring of compliance during the trial, as well as providing data that can be rapidly accessed to enable the execution of adaptive designs.

Desirable properties of devices for use in clinical trials would include:

- For **intermittent use** data devices: password protection or a form of biometric authentication to protect against use by others in place of the trial participant.
- The availability of published evidence to demonstrate that a device is able to measure the endpoint of interest to an appropriate level of accuracy and precision. It would be helpful if FDA were to provide guidance on the standards of evidence required to ensure that valid devices are selected for use.
- Encryption of data stored on the device.
- For **continuous use** data devices: the ability to post-process the data to enhance data analysis and interpretation.
- Secure data transmission methodologies, from device to database, including real-time data transmission via mobile networks or in-clinic data upload via a study portal.
- The ability to capture and combine data from a number of sensors and incorporate these to create meaningful composite endpoints. For example, using both heart rate and activity data to define individually-relevant intensity thresholds.

Wearable sensors and other remote monitoring technologies present the following opportunities:

- Generation of new more realistic patient-centric outcomes measures relating to the patient in daily living as opposed to clinic assessments (e.g., free-living activity measurement as opposed to the “6-minute walking test” performed in clinic).
- More comprehensive safety monitoring enabling a rapid understanding of patient condition between clinic visits leading to a safer trial.
- Improved understanding of patient engagement and compliance enabling escalation strategies to help encourage and retain less engaged subjects.
- Provision of objective as opposed to subjective endpoint data (e.g. sleep measurement as opposed to a subjective sleep diary) enabling greater precision and potentially powering trials with fewer patients.
- For video monitoring, continuous assessment of patient compliance (e.g., remote observation of correct inhaler technique).

Some of the potential benefits of mHealth and wearable technologies are:

- The “Patient as Sub-Investigator”TM; empowering patients to actively participate in the clinical trial.
- Improved patient recruitment and retention.
- Stronger patient engagement with their condition and its management which may carry through to routine care after the study.
- Generation of larger data sets per patient, allowing for more accurate data analyses and results.
- Better safety monitoring because of accelerated visibility of data to medical monitors.
- Better information about the effects of treatment which may benefit future patients.
- Potential for reduced time at clinic making participation more convenient.

Specifically in relation to mHealth, wearable sensors & other remote technologies, the following challenges exist:

- Cost of devices – consumer grade devices (e.g. Fitbit) are affordable but are not licensed as medical devices. Devices licensed as medical devices and thus permitted to be used to obtain critical endpoints in clinical trials are expensive, usually prohibitively so for all but small studies. We are not suggesting that the FDA regulate these devices; rather that the agency provide guidance as to acceptable data requirements for use in clinical studies.
- Lack of sponsor confidence that their data will be acceptable for establishing efficacy or safety endpoints.
- Lack of evidence that remotely captured data actually map sufficiently to the well-established endpoints that hitherto have been used to assess drug safety and efficacy.
- Difficulty in interpretation of data collected in an unsupervised setting without other contextual information.
- Identification and acceptance of appropriate data management conventions for cleaning and interpreting sensor data (e.g., the definition of the amount of data that must be collected to enable robust estimation of activity patterns in subjects or the

appropriate management of data from subjects who provide less than this minimum amount so that bias is understood and limited).

- Perceived difficulties in patient acceptance and burden.
- Devices that provide outcomes data that can be read and interpreted by the patient may lead to partial unblinding and as such may affect subject willingness to continue participating, or may influence other outcomes collected such as ePRO.
- Some devices providing outcomes data to the patient may encourage the setting of unrealistic goals and targets (e.g., a patient may attempt to improve their daily step count unrealistically).
- Logistics such as battery life, recharging, non-wear and/or problems with data capture, transmission or connectivity are all potential issues).
- For non-medical devices – firmware and software up-grades might potentially alter the device sensitivity.
- Lack of equivalence among devices may mean that data produced with one device may not be directly comparable with data from a different device.
- Device non-specific mobile applications.
- Implications of operating systems and associated operating system updates.
- Cross application corruption (e.g., smartphone cameras, GPS systems).

In addition, the use of mHealth is becoming an integral part of clinical practice in the management of certain chronic conditions (e.g., diabetes) and a return to older, less automated solutions in order to participate in a clinical trial is more likely to deter patients rather than encourage them. Specifically in relation to wearable sensors, there have been some literature evaluations on patient acceptance, in particular in relation to wear compliance. Rabinovich *et al* reported wear compliance of 79% – 91% for 14 day wear in COPD patients, with most patients identifying their willingness to wear a device for a week or longer. Notwithstanding, there may be a challenge in terms of the number of wearable sensors a patient might practically be provided with. While it is attractive to provide a single device that makes multiple measurements (e.g. a device that can measure heart rate, galvanic skin response, ECG and accelerometry), there are challenges with the use of a single device in the following ways:

- Devices may measure more parameters than we are interested in and guidance would be required on monitoring and reporting data we are not required to collect for a specific trial.
- Validation requirements will inevitably be more complex for multi-measurement devices.

Themes from ACRO members

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4. The lack of FDA regulatory guidance is hindering adoption of new technology.

Supporting material/discussions

One example where FDA regulatory guidance would be helpful, and ACRO is aware FDA has struggled with this on the commercial side of the pharmaceutical industry, is the use of social media for the purposes of patient recruitment. This can be very impactful as it can be targeted more effectively and collaboratively with one or more patient advocacy groups. One ACRO member reported this type of program generated 2,700 leads, and 400 site referrals during a 20 week program. FDA's guidance on best practices for using social media for not only patient recruitment, but to also help the industry raise awareness of clinical trial opportunities for patients.
Suggestions from ACRO members to FDA regarding providing guidance and industry communications include:

- Clarification on expectations & requirements of existing guidance e.g. e-signatures for eConsent, medical device validation requirements for wearable sensors.
- Hosting of FDA webinars, workshops and/or seminars on implementation of existing guidance on technologies in clinical trials.
- Establishment of FDA-industry expert working groups for the development of standards and guidance in those areas of technological development in which guidance is not already in place.
- Leading of discussions at the International Conference on Harmonization to generate global guidance in all of the above areas identified.
- Leading of EMA/FDA joint meeting discussions to address EU disparate positions on, for example, e-consent or the absence of guidance on mHealth and wearable sensors etc. and the impact of same on global trials.
- It would also be useful if FDA would define what evidence is needed to demonstrate that a device or sensor that has been selected for use in a study is appropriately validated. Regulatory acceptability of new technologies is uncertain until, at a minimum, the pre-IND meeting at when considerable time, effort and cost have already been expended.

Examples where limited regulatory guidance on specific innovations and particularly their use in clinical trials include:

- A subject may decide to keep notes on their device prior to completing a data capture instrument. Is that source data?

- A subject may change a device/wearable mid-trial that captures efficacy data. Should the data for that subject be questioned during inspection for potential lack of consistency?
- Principle Investigator's review and approval of the data submitted by their subjects is required under GCP – therefore a workflow is required between smartphone/web/EDC to accomplish this.
- There is a need for transparency on clinical site and subject reimbursement (e.g. data transmission fees or other BYOD – "bring your own device"- related expenses) to avoid conflict of influence.
- Guidance for IRBs on appropriate uses of social media for patient recruitment and during the clinical trials process.

Themes from ACRO members

Many of our members provided ACRO with detailed descriptions and examples of how the FDA-outlined technologies and clinical trial activities could be used to improve the drug development process. Several themes emerged from their commentary and are summarized below.

5. Data security issues need to be addressed.

Supporting material/discussions

As clinical trials collect/source/integrate/populate data from a variety of systems, data security is and will continue to be a major "sticking point" for clinical trials. The space is changing rapidly and staying on top of compliance is difficult in the increasingly complex realm of global data protection requirements. For example, the recent European Court of Justice ruling that Commission Decision 2000/520/EC10 ("Safe Harbor"), is now considered to be invalid.

While ultimately new technologies should make clinical trial participation more convenient, at present it is clear the introduction of any new methodologies in clinical trials may encroach further on patients' privacy and lifestyle. It is equally clear that such methodologies must be designed to do the exact opposite. One aspect of this that ACRO members want to highlight is that the industry should keep in mind that we still need the ability to provide direct patient support services and the associated privacy handling for new technologies. For example, FDA might want to consider:

- For intermittent-use data devices: password protection or a form of biometric authentication to protect against use by others in place of the trial participant.
- Encryption of data stored on a device.
- A plan for acknowledging the need for data security and appropriate data protection when dealing with both patient identifiable data captured in the clinic (e.g., eConsent) and data captured remotely by patients using a patient-assigned or patient-owned device.
- In addition to *21 CFR Part 11* compliance and/or regulation of certain devices as medical devices, appropriate consent by patients to the collection and processing of their data, as well as the possibility for data portability is a prerequisite for compliant implementation of all technologies in clinical trials. It is worthy of note that this has already been addressed by the eCOA (electronic clinical outcomes assessment) providers within our industry with regards to PRO data collected using mobile devices.

One aspect of data security that ACRO members would like to emphasize is the industry challenge surrounding BYOD for eCOA.

- Concerns around measurement equivalence of instruments when applied on different devices and in particular devices with different screen sizes and resolutions

- Technical concerns around the use of hardware provided by the subject, in particular relating to:
    - Issues with app usage relating to changes in device, operating system upgrade or adjusting device settings during the study (e.g. turning off notifications).
    - Issues with data security, storage and transmission – in particular the device running out of data storage capacity due to other apps and data stored on the device (e.g., music and photos), the ability to hack or access the data through other applications on the patient's device and the inability to transmit data due to hitting a data plan limit during the study.
    - Practical issues such as compensation of subjects for using their own data plans and training the subjects and sites on app access and download.

Additionally, technology vendors are accustomed to solving problems by assembling existing technology hardware and platforms. In the clinical trials industry this presents problems in data chain security and validation. In reference to wearables, for example, constructing a solution by combining medical grade solutions and consumer solutions produces concerns over data validity. A fully validated BP monitor does not necessarily combine well with a consumer-grade technology, such as a Fitbit. Morphing the industry to accept a fit-for-purpose evaluation approach would help to solve some of these issues. In the FitBit example, one cannot validate the actual number of steps for accuracy; instead one would have to use the relative number of steps to simply grade activity.

Themes from ACRO members

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6. Data integration hurdles are currently quite high.

Supporting material/discussions

ACRO members believe the future of clinical trials could hinge on the ability to integrate data from a number of disparate sources while maintaining data quality and integrity. The number of potential data sources to be captured in clinical trials is rapidly increasing and protocols are being designed to capture a wider and deeper set of variables. Data integration will be a core competency of any pharmaceutical company/service provider in the very near future.

One ACRO member is working on a pilot study with a sponsor and a third-party vendor system to create a bridge between Electronic Health Record (EHR) systems at research sites and a leading EDC provider. The advantages of this approach allow a custom level of integration for sites with different EHR system capabilities or no EHR system at all. It also facilitates keeping all of the clinical data in one system with the advantages of eSource where available and still providing the ability to leverage all of the standard system integrations, such as IXRS, ePRO/eCOA, CTMS and Safety with the EDC system(s). The greatest challenge with this effort is getting sites to allow a connection to their Electronic Health Record systems if they are not already using the Clinical Operating System for its primary purpose. This company has executed six studies, five of which have locked using a tablet-based data capture. This tool allowed most data in the study to be classified as eSource and greatly reduced the source verification and other typical data cleaning activities. The greatest challenge was introducing a new device into the sites electronic ecosystem that required access to the internet and this created some adoption challenges for some clinical site locations.

Another ACRO member is in the initial stage of a pilot with a sponsor that will utilize the CDISC EHR initiative to connect EHR data to EDC.

FDA can play a vital role in providing clarity on how the industry can mitigate against “dirty data.” Real World Data (RWD), often sourced from EHRs, represents a huge opportunity for our industry. That said, if the same level of data cleanliness and the consistency of traditional approaches is required, then using RWD analysis will fall short of its potential. If our industry can recognize that large data sets of less clean data can be as useful as smaller data sets of extremely clean data, then we could make full use of EHRs – both in terms of cost of collection as well as the broadening of the definition of a “clinical/investigative site.” ACRO members understand that this may require a different

approach to designing studies (statistics, approach to CRF fields, etc.) and we would like to engage with FDA to provide our input into future guidance.

Another integration challenge surrounds endpoint identification and validation. The ability to capture and combine data from a number of sensors and incorporate these to create meaningful composite endpoints will be necessary for innovative data collection methodologies to move forward. For example, using both heart rate and activity data to define individually-relevant intensity thresholds. Variability of data structures within systems has, for years, created a barrier to effective integrations of systems. The need for effective standards adoption is essential for both sponsors and other organizations involved in clinical trials and it is the only way to create the speed and reusable forms and systems that sponsors need.

As a final note on this topic, our industry should be cognizant of the new world we are playing in. Many of the startups and new contributors to new technology are not experienced in working in the tightly regulated and conservative world of clinical trials. They are more experienced in working in standard technology application development environments and thus not as well versed in the validation of technology as applied in clinical trials. Even if they are experienced in developing consumer-driven health applications their lack of vendor experience in clinical trials and the absence of standard SOPs makes passing a standard CRO's validation difficult. This is one area FDA can provide guidance and a platform from which technology vendors, sponsors and CROs can all work together.

Themes from ACRO members

Many of our members provided ACRO with detailed descriptions and examples of how the FDA-outlined technologies and clinical trial activities could be used to improve the drug development process. Several themes emerged from their commentary and are summarized below.

7. Change management is currently, and will continue to be, a necessary skill set to have before widespread adoption of new technology and processes are accepted. Technology is changing faster than the industry can change to take advantage of it.

Supporting material/discussions

ACRO members believe the industry is in the midst of an era of rapid change, driven by technology. The change will be much more drastic than simply “e-ifying” paper processes (e.g. moving from paper CRFs to EDC). Enter change management.

Change within a sponsor organization offers one challenge. Change within service providers offers another challenge. Change within clinical sites offers yet a third challenge. The industry cannot underestimate the increased complexity for investigators and site staff and we must, as an industry, train them to support patients in the use of new technologies. Another real-world impact of change is the question of how capable and qualified Institutional Review Boards (IRBs) are to quickly and adequately assess clinical trial technologies and make a determination about their appropriate application.

Today, technology is used and accepted by most people in most spheres of their lives and at this time clinical trials are lagging behind sectors such as banking in replacing slow old paper-based processes with modern Information and Communication Technology-based (ICT) systems.

Conquering the change management challenge will be essential if the industry is going to move forward at any reasonable pace. Clinical trial sponsors, CROs and researchers all have tried-and-trusted approaches to executing studies. Adding in new methods means adding in solutions that may contain cost and risk issues into study timelines or data collection. In the competitive landscape of clinical trials this is a difficult problem to address. Many stakeholders, while supportive in general, simply do not want to take the risk to move the process forward on their specific trial or program. Further issues around site training, patient training and scalability start to emerge as the application of technology grows. For example, incorporating an iPhone application in an indication where patient demographics are in the 20s to 40s presents very different training needs than that of a geriatric study where there may be significant knowledge gaps.

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8. The continued improvement in access to near-real time clinical trial data will open up possibilities that could dramatically improve patient safety and improve trial efficiencies.

Supporting material/discussions

The continual evolution and pervasiveness of the internet and telecommunications-connected devices has enabled the real-time collection and reporting of clinical trial data. We are entering a stage in clinical development where the CRF is likely to hold less and less source data. We are also moving from a world of batch-processing system for data entry and cleaning into one where data is continuously collected and visually made available to clinical trial professionals in near-real time. These data could come from ePRO/eCOA systems, EMRs, activity monitors, labs, wearable sensors, and/or from home-based telehealth/monitoring systems. The ability to collect data on trial participants between clinic visits provides important additional information about the effects of treatment and can supplement and sometimes replace data recorded during visits to study sites. In addition, real-time access to these data enhances both subject safety and the monitoring of compliance during the trial, as well as providing data that can be rapidly accessed to enable the execution of adaptive designs.

While the opportunity to collect more data, and maybe higher quality data, holds a lot of potential for clinical researchers, it drastically adds to the complexity/scenarios for data collection. One example that was given at a recent conference sums up how collecting data from non-CRF sources could impact clinical trial operations. In this example a man is wearing a patch on his chest to monitor heart rate and ECG readings and transmits data every few seconds. What if he is walking in New York City and he enters a spot where his patch cannot communicate with a cell tower? What is the protocol? Does he need to be contacted, and if so, how? How long can the patch be “down” before someone has to take action? Does someone have to be continuously monitoring the data flow if the flow of data is continuous? Does there need to be a GPS-enabled device with him so someone can find him should a problem be identified in the data? Are there potential issues to work through? Yes. But the potential positive impacts on patient safety and scientific discoveries far outweigh the downsides and we, as an industry, need to actively lead this effort and not allow our industry to fall further behind the technology curve.

Within the past year, a number of ACRO members have formed a dedicated innovation team. Generally, the mission of these teams is to identify, evaluate and enable the application of innovative capabilities and solutions that add value and transform clinical

development in the pharmaceutical industry. As these teams have reached out to sponsor partners, they have found that many large pharma companies are also focusing on innovation within clinical development. They recognize that improving the success and efficiency of clinical trials depends on leveraging technology and innovation to improve the patient experience and increase the accuracy and frequency of data collection. They have found that in many larger pharma organizations the appetite for innovation is present but the aforementioned challenges in change management still hamper the rate of adoption. ACRO members are seeing a groundswell of interest within large and small pharma sponsors that are working to make the necessary process changes to enable the adoption of new technologies to bring about greater efficiency.

Combining multiple ways to capture data (e.g., integrating data sources including EDC, ePRO, labs, or eCRFs as source), along with real time visualizations of this data, have been widely adopted within the CRO industry. Advances in technology, and more specifically business intelligence and visual analytics tools and associated techniques powered by innovative platforms are revolutionizing the management of data for clinical trials and beyond. With the ability to visualize multisource data including those previously untapped, clinical and medical personnel can achieve faster insights into the data and hone in on key areas to facilitate expedited review and decision making and thereby improve trial safety, quality and efficiency. What is lacking are data standards (structure of data, integration, definition of variables) and guidance (endpoints, acceptance, working groups) to ensure data collected will be accepted by the regulatory bodies.

With all of the advancements in technology, we need to be mindful of the most important relationship that drives clinical research – the relationship between the patient and the principal investigator. There is no substitute. Remote technologies could be used “beyond the pill” where devices could facilitate primary care givers to identify clinically significant changes that may not be apparent during a routine clinic visit, thus identifying at risk patients in their home setting and allowing for earlier intervention. The link between the investigator and patient is of primary importance, as many patients report that their participation in a study is heavily influenced by the relationships they have with site staff. As the duration of a study lengthens, or the study becomes more challenging for a patient, those relationships are key to reliable outcomes. Nearly all feedback from patients indicates that they want improved treatment options and overwhelmingly value the direct contact with investigators and study staff as part of their perception of the study’s quality.

The ability to collect vast quantities of data from multiple sources in near-real time is just the beginning. The ability gets us started, but the industry needs help to move to the next steps.

- How should one capture these data?
- Who should see the data?
- How does one monitor the data?
- How does one store the data?
- How does one analyze the data?
- How does one validate the data?
- How much data is enough?

- How does one integrate the data?
- How does it change when looking at interventional vs. non-interventional studies?
- What are the best methods to protect privacy and ensure data protection?

Drug innovator companies, CROs, technology companies and FDA need to all work tougher to help move clinical development forward in order to unlock the value new technologies enable.

ACRO looks forward to being a resource to the agency as it moves ahead to promote the use and adoption of innovative new technologies and clinical trial methods.

Respectfully submitted,

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