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In the next issue of
EDC Today:

EDC and Adaptive
Trial Design

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Is it EDC or is it eCRF?

EDC Today is an independent publication on current information and issues in Electronic Clinical Systems (ECS) strategies and technologies for the Biotechnology and Pharmaceutical (Biopharma) industry. Each month we examine topics related to ECS theory, technology, practice, or implementation.

EDC Management is often party to interesting discussions concerning EDC and its adoption by Biopharmas. Recently, we were fascinated by an electronic conversation held by Chris Connor of Health Industry Insights in which he posed a question about the future of EDC, asking whether or not it had “jumped the shark”¹ and whether or not EDC was on its way to widespread adoption.

In this issue, we present some highlights of the discussion as well as a theory concerning why EDC software has seemed to be slow in gaining ground in the Biopharma world; a theory spawned when the discussion took an interesting turn when T. J. Kuhn asked and expanded upon what he meant by “is it EDC or is it eCRF”²?

Introduction

Entering the brave new world of electronic discussion, we at EDC Management encountered one that we found most intriguing. This new world has its own lingo, so the eye catching reference to whether or not EDC had “jumped the shark” caught and held our attention and made us think. First, we had to determine what it meant for EDC to have jumped a shark. We at EDC Management initially thought it might mean getting past the dangerous point in its development where so many software development efforts fail. However, we learned that the term doesn’t mean that at all. In fact,

“Jump the shark or jumping the shark [was] a term originally used as a metaphor for when a television series has passed its sell-by date. The term originated after an episode of the hit television series Happy Days. In one episode, Arthur Fonzarelli, otherwise known as The Fonz, literally water skis over a shark. It was at this point that viewers became disenchanted with the show and its days were numbered.”³

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So the question put to us is more plainly phrased, “Has EDC reached and passed its peak?”

T. J. Kuhn went on to say

“I have been thinking about eDC a lot of late, mostly because what is commonly called eDC is not eDC.”

What he means by this is that what so many people are calling EDC is actually an application that presents one or more electronic Case Report Forms (eCRF), and he defines eCRF as being:

“...an electronic form that does the same thing a paper CRF does. The clinical site types the data into an electronic form that gets electronically submitted to the sponsor. Essentially, the sponsor is removing a (paper-based) step and pushing the data entry from their internal (Data Management) group to the clinical site. That’s eCRF.”

While an eCRF “presentation application” probably includes real-time error checking and often autoencoding entries using a dictionary as well as varying levels of other automation, it isn’t really EDC. What he calls EDC:

“...deals with data being recorded as source in an electronic format. That means that it isn’t written in a paper medical chart. The first time it is recorded (in any manner) it is recorded electronically.”

An example familiar to most of us would be a blood serum or urine analysis laboratory machine that automatically transmits the results from the requested tests to a computer system after it performs the analyses. Ideally, EDC would also include such data as the results of a physical exam that are directly typed into a computer system and not first written to a patient chart or other form.

The terms EDC and eCRF seem to be used interchangeably in the clinical workspace with nearly everyone using the term EDC even though there are very few implementations of what T. J. Kuhn, and those like us at EDC Management that accept his definition, would label “True EDC.”

Has EDC Jumped the Shark?

Returning to Chris Conner’s original question asking if EDC has peaked, if we use T. J. Kuhn’s definition, the obvious answer to the question is emphatically “no” and likewise, the answer to whether eCRF has peaked is only slightly less emphatically “no.”

EDC (or eCRF) vendors haven’t yet begun to scratch the surface of what is possible and there are still years of development and refinements to be done. The benefits, if “True EDC” is ever achieved, will probably be remarkable. The cost of getting there will, unfortunately, be equally remarkable.

Biopharmas are very conservative when it comes to implementing new approaches and new technology. They have been slow to adopt eCRF applications and they will be slower to adopt

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“True EDC”. T. J. Kuhn expressed the opinion that the small Biopharmas that traditionally follow the lead of bigger Biopharma companies will lead the way to “True EDC”. That may be so, but we at EDC Management aren’t sold on that opinion.

As a follow up question, Chris Conner asked if EDC was an “interim technology”. Given the nature of technological change, of course EDC is an “interim technology”. All technologies are “interim” in the long term. However, we at EDC Management think he was asking if EDC is going to be viewed as a fad or if it will be absorbed into our life in a manner much like the telephone, with huge and lasting impact. That is an interesting question. Where things will go, insofar as what technology will be used during the conduct of clinical trials in the future, is impossible to guess with any amount of confidence. What hampers our ability to “peer into the crystal ball” is not knowing what technological innovation might arise tomorrow and how they will eventually wind up being regulated in the tightly regulated field of clinical research. Some of the many issues that hamper the development of EDC or eCRF applications however, can be assessed.

What is Hampering EDC?

EDC applications, and their underlying CTMS, if any, are always slowly evolving to include newly mandated requirements from regulatory authorities. Being large, fairly complex products, it can take a year or more to write or extensively revise an EDC "application".

Absorbing these regulatory "compliance" issues and applying them to an EDC application has involved penetrating the often murky, ill-defined regulatory requirement(s) and coming to a Biopharma industry-wide consensus as well as agreement with the regulatory bodies as to exactly what is intended by the regulation, and gaining sufficient comprehension of what needs to be implemented. Doing this takes time.

For example, the first regulatory rumblings concerning electronic signatures surfaced in 1991. It took six years for the 21 CFR part 11 final ruling to be published on March 20, 1997.

Compliance with Part 11 requires that an organization have a fully functioning quality assurance infrastructure in place. It is not possible for computer hardware and software to be compliant out-of-the-box. This is because automated systems must fit into an organization as part of a larger quality system, which entails much more than just the code itself. The most important element of Part 11 compliance is a firm's written policy on Part 11. A firm's written policy on Part 11 is the cornerstone of, and will set the tone for, Part 11 compliance. The policy will dictate which systems will need to be Part 11 compliant and how the validation of these systems will take place. No two FDA regulated companies do exactly the same thing in the way.⁴

Last year, in 2007, sections of 21 CFR part 11 were challenged as excessive, and the FDA stated in guidance that it will exercise enforcement discretion on many parts of the rule. This has led to even more confusion on exactly what is required.

An EDC vendor has had their hands full trying to keep their product in step with just regulation 21 CFR part 11 and has had them full for nearly fifteen years with more to come!

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They have been further hindered by other government regulations – for example, those concerning CDISC and the use of its standards with electronic submissions. CDISC standards have been slow in taking shape mainly for political reasons as opposed to technological ones. Fortunately, their day has arrived and their long gestation is now at end.

As technological development leads the industry to change the way it does things, new or modified regulations have been needed, and the software application development has been partly paralyzed because of this.

EDC and EMR

One of the largest remaining challenges to “True EDC” is its interoperating with the myriad of slowly emerging electronic medical record systems (EMR) which face the same issues that EDC systems have. One of the largest of these issues is compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

HIPAA called upon the Department of Health and Human Services (HHS) to publish new rules that will ensure:

- Standardization of electronic patient health, administrative and financial data
- Unique health identifiers for individuals, employers, health plans and health care providers
- Security standards protecting the confidentiality and integrity of "individually identifiable health information," past, present or future

The parallelism with EDC and 21 CFR part 11 is almost disconcerting.

Another challenge to EDC vendors is how to approach Adaptive Trial Design. This remains largely to be seen. To quote Michael A. Martorelli, of Fairmount Investment Partners:

"It is not fair to criticize the drug industry for not rushing to embrace adaptive trial design, and we are not doing so in this commentary. We understand all too well that in the highly regulated business of conducting clinical trials, sponsors are reluctant to get ahead of the FDA in adapting any new procedure, test, technique or process."⁵

The regulatory agency paralyzes development efforts when the trade newspapers announce things such as

"In the United States, the FDA has indicated its desire to publish a guidance document on the use of adaptive trial designs some time in 2008."⁶

Conclusion

This entire newsletter sprung from the fertile grounds of the brave new world of electronic discussion. It barely contains an interesting swirl of fresh ideas and refinements to how concepts can be described and how they might work. It takes a little bit of effort to understand the language and to find the right places, but we believe the effort is well-spent.

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Is it EDC or eCRF? - The distinction is an important one but in the end, we feel it all comes down to when eCRF applications will be transformed into "True EDC" applications. In any event, whatever you call it, the technology has caught root, and will be growing and evolving for quite some time. The frustrations with the slowness of its evolution can be somewhat assuaged by the understanding that the slowness is partly based on the complexity of the application, significant development cost, and by the slowness in which regulations are promulgated and refined.

We think attaining true EDC should be the long term goal and doing so will mean having interoperability with EMR systems. In fact, we think that in order for EDC to become "True EDC," it may need to become an "add-on" module to existing EMR systems. In any event, how such a thing is achieved and implemented will take some brilliant thinking and a lot of patience by application developers and all of its stakeholders.

It may be too much to ask for, but if the regulatory process could be made more timely and responsive, it would take considerably less patience and allow those aforementioned brilliant minds to find the ways to the future of EDC.

Resources

¹ <http://www.linkedin.com/answers?viewQuestion=&questionID=189746&askerID=9462204>

² <http://tjkuhn.wordpress.com/2008/03/14/the-difference-between-edc-and-ecrf/>

³ <http://www.wisegeek.com/what-does-it-mean-to-jump-the-shark.htm>

⁴ <http://www.automation.com/resources-tools/articles-white-papers/fda-validation/about-21-cfr-part-11-electronic-records-electronic-signatures>

⁵ Martorelli, Michael A. (2008 June 17). *Outsourcing Industry Monitor*, Fairmount Partners, 5.

⁶ *ibid*



Who's behind the research?

Our lead researcher, Kirk Mousley, PhD received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

Karl Mousley received his BS in Mechanical Engineering from Rose-Hulman Institute of Technology and a MS in Computer Science from Villanova University. He has been a senior member of the technical staff at Mousley Consulting, Inc. since 1993. Among his significant accomplishments are the investigation, evaluation, and implementation of new computer technologies for clinical data management systems and developing strategic plans for integrating these technologies into current systems. He has extensive experience preparing Standard Operating Procedures (SOPs).



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