

Written and researched by:
Dr. Kirk Mousley
and Karl Mousley

Considerations for International EDC Deployment

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.

Recently some of the staff at EDC Management had the opportunity to work on implementing an EDC study in which investigator sites from a number of countries are involved. The work was interesting in that each day brought new challenges due to cultural differences such as language used in functional specifications and the prompts on the eCRFs. Delving deeper into the project brought to light other challenges, some of them quite unexpected.

In this issue, we discuss some of the challenges of deploying EDC internationally; challenges that add another layer of complexity with which our readers that perform international clinical studies with paper CRFs are already familiar. We will discuss some obvious “snags” and some less obvious ones – being aware of these issues is but a start on the road to successful international EDC deployment.

I. Introduction

There are a number of issues involved with the use of EDC systems on an international basis. They range from having roots in cultural differences to those with roots in the technical aspects of computerization. Some of these issues are not specifically related to EDC, but are applicable to any data collection effort, and are due in part to long-standing differences between countries over how things are done.

In the next issue of
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EDC Management

P.O. Box 384
Conshohocken, PA 19428
484-530-0300 (voice)
610-567-0357 (fax)
info@edcmanagement.com
www.edcmanagement.com



It is perhaps unfortunate, but the United States of America, one of the largest marketplaces for biopharma products, differs largely in how it does things from most other members of the global community. Many of these differences stem from its colonial days when the USA attempted to differentiate itself from its British rulers. Apparently baseless differences, such as which side of the road to drive on, the direction a Merry-Go-Round turns, the side on which to mount a horse, color of its currency, and to a degree, even with the English language, served to assert independence from England. Nowadays, the differences may be more of a nuisance than sensible.

It is important to note that while we don't go into other types of concerns in this issue, such as attempting to comply with multitudinous and perhaps contradictory regulatory requirements, or even more pragmatic logistical difficulties of getting materials like the study agent (drug), CRFs, and computer equipment delivered across national boundaries, these burdensome issues also exist.

II. Language

Even with paper-based CRFs, cultural differences cause many problems with conducting multinational clinical trials, language being the most obvious difference. The difficulty of wording technical prose such as Protocols and CRF prompts is compounded when they need to be translated into a different language. There is a lot more to translation than transliteration, and translation is a task best left to the experts in the field. In addition to translation, effort must be spent on developing and maintaining language-specific versions of Codelists and Dictionaries, such as those used for medical terminology encoding. EDC system software may need to be enhanced to support the use of multiple languages and coding systems, as many of them do not have that capability. If your EDC application doesn't support multiple languages, for an international clinical trial you may need to develop and maintain an entry system for every language your investigators use.

Furthermore, some languages do not use the basic Roman 26-character alphabet. For paper-based CRF, this means printing the CRF is more complicated. The situation is even more complicated for computer-based representation of these characters. Much like medical terminology, individual characters are coded when stored in a computer system, and supporting multiple character sets adds a layer of complexity to a computer system.

One obstacle to using different character sets is determining how the characters will sort. For example, a sort order specifies the rules used by the database server to interpret, collate, compare, and present character data. For example, a sort order defines whether the Arabic character 'i' is less than, equal to, or greater than 'i'. It also defines whether the collation is accent-sensitive (for example, whether 'i' is equal or is not equal to 'i').

Thus, even prosaic activities are impacted by multi-language/multi-alphabet support; activities such as database queries may need careful consideration in order to be accurate and successful.

To complicate this further, some Relational Database Management Systems (RDMS) like Oracle may require you to select a "code page" to be used by the database when it is set up. Selecting the wrong "code page" may mean you will be unable to database the data you capture from other countries. Likewise, the server that presents eCRFs to your investigators will also need to be properly configured in order to display characters in the language used by your investigators.

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III. Units of Measurement

While most of the world has embraced the International System of Units (SI) known as the modern metric system, the USA stubbornly resists such a change. While many “scientific” or “technical” professionals in the United States perform their work using SI units, not all measurements found on a typical CRF used within the US will be measured using standard SI units; a subject’s height (inches) and weight (pounds) being typical examples. Even in areas that are fairly global in nature, such as blood, urine, or other laboratory measures, differences in units of measure remain. The FDA has, in the past, expected laboratory measurements to be reported to them in certain units, and those units differed from those expected by European regulatory bodies. As a result of the efforts of the ICH and others, eventually nearly all regulatory bodies will embrace a common SI-based unit of measure for all common measurements found on a CRF.

IV. Health Care Practices and Standards

Many countries have health care practices and standards that differ from other countries. Some countries, such as Canada, offer national medicine that is a sharp contrast to the USA’s health insurance/HMO/Medicare hodgepodge. Undeveloped countries may not have permanent health care facilities at all. These differences affect how clinical trials are conducted as well as the desirability of conducting a clinical trial in any given country.

V. Formats of Dates, Numbers, and Currency

An important thing to consider when selecting an EDC system is how responsive it is to the user. This responsiveness is commonly measured in “page turn rate”. One common way to enhance the “page turn rate” is to perform all the data validation on the client, that is, execute validation scripts on the user’s computer. This may lead to an unexpected situation where the scripting language uses the user’s computer’s “regional settings”. Scripts executed server-side, while possibly less responsive to the user, might have the advantage of a consistent data environment.

To explain what is meant by this more fully, we will explore the “Regional Options” for a Microsoft Windows personal computer. This applet can be found within the Control Panel. Launching the applet brings up a dialogue box with a number of tabs.

On the tab labeled “General” you will find “Locale”. The locale (location) is used to determine the default settings for that region, such as time and date formats. You may notice there are a number of Language settings, which configure the computer’s code pages (e.g., the codes used to represent letters, numbers and special characters).

On the tab labeled “Numbers” you will find settings for the symbol used to indicate the decimal (e.g., the period in the USA, a comma in France) and the decimal grouping symbol (e.g., the comma in the USA, a period in France!), and the measurement system (U.S. or Metric).

On the tab labeled “Currency” you will find the currency symbol setting (“\$” in the USA, and “€” symbol for Euros, amongst others). This setting should rarely be an issue with EDC and CDMSs, but a Clinical Trial Management System that reimburses investigators should be, and normally will be, designed to avoid it. If you do a lot of work in Excel, you may have noticed that formatting a cell or column as “Currency” places the currency symbol in front of the entered number(s). “Regional Options/Currency” is where the symbol used by default in Excel comes from.

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On the tab labeled “Time” you will notice that countries like France commonly use the 24-hour “military” time format as opposed to the 12-hour AM/PM format commonly used in the USA.

On the tab labeled “Date” you will find a plethora of date formats. Programmatically speaking, date data can be the most cumbersome to deal with because of the variability of format. Setting aside the “long date” formats with their language differences (for names of days and months), the short format using the slash “/” symbol has two primary versions; day / month / year format used in Europe and the month / day / year format used in the USA.

Note:

If you explore the various “Regional Option” settings, please remember to click on the “Cancel” button when you close down the applet. These settings most likely should not be altered on a permanent basis.

Your computer often uses these “Regional Option” settings when it executes scripts and programs. One client-side scripting language commonly used by EDC systems is called Visual Basic (VB). VB, and other scripting languages, depend on default formats and/or regional settings when processing data. Given a date in the form of characters, such as “02/03/2005”, VB will attempt to convert this into its internal format for a date. Using the Regional Option setting for short date format could be disastrous! This date for an American investigator is February 3rd, 2005 whereas for a European investigator it is March 2nd, 2005. A VB data validation script may not behave as expected. Worse yet, problems such as this situation are very difficult to catch while testing scripts. What works for the tester might not work for the end user and vice versa.

VI. Other Cultural Differences

When designing your EDC and/or Portal page(s) make sure the content of your site is written in plain, easy-to-understand language. Avoid using many abbreviations, colloquialisms or idioms. Plays-on-words, humor, or pop-culture references may be lost on your visitors. The graphic scheme used by your Web pages should use “a few popular, business-like colors. Because colors and color combinations are loaded with meaning (especially in Asian countries), using too many strong colors such as red or yellow may send unintended messages to your visitors.”¹ Likewise, make sure your Web pages look good when printed on A4 paper-size (it’s longer and thinner than the Letter size used in the USA). When generating a printed copy of a CRF page, it should be formatted to fit the default paper size of the user, and in most countries, the standard paper size is A4.

VII. Conclusion

If you are planning to use EDC to conduct a study with investigator sites in a number of countries, you may want to develop a strategy for how you will deal with issues due to cultural differences.² Your strategy might be to use English only, SI units, and a specific date format that is clear to all. This strategy will not necessarily avoid all the problems encountered when internationalizing a trial, but it might serve as a starting point when developing a more complete strategy.

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Obviously it is important to get qualified translators to translate documentation sent to an investigator whose primary language differs from yours. Less obvious will be the need for your clinical trial managers, helpdesk and other support people to be able to communicate with all of your investigators. Awareness of the investigator's regulatory concerns, work practices, and other cultural differences will be important. Even investigator site time zones and possible siesta split work shifts might come into play.

Be alert to different preferences as far as units of measurement and make plans to convert values when necessary. Take care with your Web site(s) color schemes and graphic content. Be alert to seemingly trivial issues such as paper sizes used by printers.

You will probably want to investigate how well your current or prospective EDC vendor supports internationalization. There are EDC systems with built-in support for designing CRF pages with prompts in multiple languages (most likely offered by European vendors due to the demands of their local market), and some EDC systems can even support the automatic selection of language based on the user's computer locale, as set in the Regional Option.

Furthermore, you might want to determine how well (or poorly) your current or prospective EDC system deals with issues arising from regional differences; particularly data validation if it is run on client computers.

Hopefully this issue has provided an introduction to some of the various pitfalls and complications of conducting an international clinical trial. It is by no means comprehensive, and we encourage comments from our readers about their experiences with the cultural differences that make human beings a diverse lot, and with their experiences with EDC across national boundaries.

In an upcoming issue of EDC Today, we plan to present users' experiences with EDC. To help us more fully understand your experience with EDC, we've developed an online questionnaire. If you've used EDC, we hope you'll take a few minutes to answer our questions. Just click the link below or type "<http://www.edcmanagement.com/questionnaire.asp>" into your browser to access the questionnaire. Your participation is appreciated!

**YES, I'd like to participate
in your online survey**

References:

¹ <http://www.mamercado.com/Internationalizing%20Online-FM6-02.pdf>

² <http://www.rubric.com> - "A Guide to Localization Management" White Paper.



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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