Electronic Data Capture (EDC)

How UC Davis Can Benefit From EDC

Jules T. Mitchel, MBA, Ph.D.
(julesmitchel@targethealth.com)
Target Health Inc.

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A Touch of Philosophy

Every truth passes through three stages before it is recognized:

In the first it is ridiculed
In the second it is opposed
In the third it is regarded as self-evident

(Arthur Schopenhauer)
A Touch of Philosophy

What a person hears he/she may doubt

What he/she sees, he/she may possibly doubt

But what he/she does, cannot be doubted

(Adapted from Seaman Knapp: American Agriculturist and Educator)
The Problem

- How the customer explained it
- How the Project Leader understood it
- How the Analyst designed it
- How the Programmer wrote it
- How the Business Consultant described it

- How the project was documented
- What operations installed
- How the customer was billed
- How it was supported
- What the customer really needed
Why Electronic Data Capture (EDC)?
Business Case For EDC

- When used properly, time to database lock per study can occur in days compared to months when using paper CRF-based systems.

- When data are entered promptly, problems associated with a clinical trial can be identified and rectified early.
EDC FEATURES

- Edit checks fire at the time of data entry
- Online batch edit checks
- Query management
- Audit trail of changes
- Email alerts (e.g.: liver enzymes 5X ULN)
- Central randomization
- Central laboratory integration
- Electronic signatures
- Data management reports
- Project management reports
Infrastructure

- No Software Installation
- Offsite housing of production servers
- Redundant power and connectivity
- Real time replication of data
- Daily backups
- Offsite weekly backups
- Full SOPs
Cost Savings

- There is no need to create paper CRFs
- There is no printing of CRFs
- There is no shipping of original CRFs to the sponsor from the study sites
- There is no logging in of completed CRFs
- There is no double-key data entry
Cost Savings

- There is no resolution of key stroke errors during double-key data entry
- There are no illegible fields to query
- There is no QC of double-key entered data against paper CRFs
- There are minimal offline batch edit checks as cross-form and batch edit checks can be run within EDC systems
Cost Savings

- There is no storage or archiving of paper CRFs
- Queries are tracked electronically and reduced by 50%
- CRFs are signed electronically
- Monitoring is done online
- If planned properly, database lock can occur within one week of last patient last visit monitored
IT IS ALL ABOUT DATA
Impact of Pre and Post SDV
Mean and SD Values Do Not Change

- Data were collected from 40,000 records of 492 randomized subjects with BPH.

- Queries were generated based on edit checks that fired at the time of data entry and on online edit checks run in a batch mode within the EDC system.

- Each data element change was subject to an electronic audit trail and for each modification, a reason for change was required.

- In order to evaluate the impact of data changes on the data analysis, an assessment was made of 331 data changes of 5 numeric variables contained within 1,287 uroflowmetry forms.
Objectives

1. Identify the number of changes made to a clinical trial database using EDC

2. Evaluate the reasons for change

3. Assess the value of source document verification (SDV)

4. Provide recommendations to optimize monitoring of clinical trials
Methods

Target e*CRF was used as the EDC tool for a multinational, dose-finding, multi-center, double-blind, randomized, parallel, placebo-controlled trial to investigate efficacy and safety of a treatment in men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)

- Data were collected from 566 subjects who signed informed consent and 492 subjects who were randomized to treatment
Methods

- eCRFs were monitored both prior to onsite monitoring and at the time of source document verification (SDV)

- Queries were generated based on edit checks that fired at the time of data entry, edit checks that fired in a batch mode within the EDC system, and based on findings during onsite monitoring

- Each data element change of a form was subject to audit trail and for each form modification, a reason for change was required

- A decision was made to cut off the analysis after at least 40,000 forms were entered
Methods

- Reasons for change to the database included:
  - Additional Information
  - Entry Error and
  - Other, Specify

- Changes could include one change or multiple changes per form

- Site coordinators were trained on:
  - Functionalities of the EDC system
  - CRF completion guidelines
Results

There were a total of 2,584 (6.22%) changes to 41,568 forms.

Changes were designated by the sites as:

- **Data entry errors:** 71.1%  (n = 1,836)
- **Additional information:** 18.8%  (n = 486)
- **Other reasons:** 10.1%  (n = 262)
Just a Few Forms Drove Most Changes

- 84% percent of all changes occurred in 10 of 27 (37%) forms

- 71.5% of all changes occurred in just 6 of 27 (22%) forms

- Of the 2,584 changes to the database:
  - 20.8% occurred in the Micturition Diary Log
  - 13.9% in the Medication form
  - 12.6% in the Illness (medical history) form
# Examples of Changes

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<th>Screening No.</th>
<th>Maximum Flow Rate</th>
<th>Average Flow Rate</th>
<th>Voiding Time</th>
<th>Flow Time</th>
<th>Voided Volume</th>
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<tr>
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<td>12</td>
<td>5,7</td>
<td>44,9</td>
<td>6,7</td>
<td>282,6</td>
</tr>
</tbody>
</table>
Medications

- Trade Name changed from Timolol to Timolol 0.5%
- Ongoing changed from Yes to blank (entered as Sponsor Request)
- Dose Per Administration changed from 1000 to 81 (Mg in Unit; Fish Oil in Trade Name) (Additional Information)
- Dose Per Administration changed from 2 to 600/800; Unit changed from Tablets to Mg (Additional Information)
- Dose Per Administration changed from 75 to .075 (Entry Error)
Medications

Some examples of changes in the Indication field:

- Runny Nose to AE upper respiratory infection (Additional Information)
- Hoarseness to GERD (Entry Error)
- Right Shoulder Pain to Right Shoulder Pain And Arthritis (Entry Error)
- Arthritis to Arthritis and Herpes Zoster (Additional Information)
- Arthritic Pain Management to Arthritis (Additional Information)
Adverse Events

- Adverse Event changed from mastitis to gynecomastia (Additional Information)
- Serious changed from Yes to No (Entry Error)
- Intensity changed from Mild to Moderate (Entry Error)
- Other Action Specify changed from blank to Cipro (Entry Error)
- Relation changed from Unrelated to Possible (Additional Information)
Averse Events

- Adverse Event changed from Soreness At Injection Site to Soreness At Injection Site, Right Upper Quadrant (Additional Information)

- Adverse Event changed from Swelling, [Drug Name] Injection Site RXN Left Lower Quadrant Abdomen to Swelling, Injection Site Left Lower Quadrant Abdomen (Entry Error)

- Adverse Event changed from Depression-Headache to Depression (Other)
Changes to Demographics

In spite of this being a study in males with BPH, gender was a data entry field in the demographics form.

Strikingly, one of the database changes was from “FEMALE” to “MALE”.

Other changes were to the month and date of birth. In one instance, the year of birth was changed from 1950 to 1945.
Conclusions

Source document verification (SDV) of original clinical trial data was mostly needed to resolve transcription errors from paper source documents to the EDC database, although some systemic errors were observed.

Aspects of monitoring could be performed remotely by observing and then resolving errors such as how to describe an injection site reaction.
Conclusions

By reviewing trends of online and batch edit check hits early in the clinical trial, field monitoring and data entry errors can be dramatically reduced.

Training and retraining of the sites and assurance of protocol compliance then becomes the focus of monitoring rather than SDV of original data.
Conclusions

If the clinical research sites could perform direct data entry and bypass the use of paper source documents as original data, and the pharmaceutical industry follows a “Rational Monitoring Plan (RMP)”, there is the real possibility to:

- Reduce unnecessary busy work
- Increase the quality of clinical trial data
- Reduce the time to database lock
- Stop development of ineffective and/or unsafe drugs early
- Accelerate time to market
FDA Gifts to Say Goodbye to Paper

- 2007 Guidance on Computerized Systems Used in Clinical Investigations
- 2010 Guidance for Industry Electronic Source Documentation in Clinical Investigations
- 2011 Guidance for Industry Oversight of Clinical Investigations A Risk-Based Approach to Monitoring
Applies when source documentation is:

- Created in hardcopy and later entered into a computerized system

- *Recorded by direct entry into a computerized system*
Original Data

Original data are those values that represent the first recording of study data.

FDA is allowing original documents and the original data recorded on those documents to be replaced by copies provided the copies are identical and have been verified as such (see FDA Compliance Policy Guide # 7150.13).
A certified copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.
New Draft Guidance - eSource

Guidance for Industry Electronic Source Documentation in Clinical Investigations

December 2010

Why Did FDA Write the Guidance?

Advantages of electronic platform

- Eliminate unnecessary duplication of data
- Reduce transcription errors
- Promote real time entry of data during visits
- Prompts for missing data and data errors will ensure accuracy and completeness
- Potential interface with medical devices, electronic health records, laboratory data, imaging systems, etc.
- Rigorous audit trail
New Draft Guidance - Monitoring

Guidance for Industry
Oversight of Clinical Investigations
A Risk-Based Approach to Monitoring

August 2011

New Draft Guidance - Monitoring

FDA recognized that data from critical outcome studies (e.g., NIH-sponsored trials, MRC-sponsored trials in the UK, International Study of Infarct Survival), which had no regular on-site monitoring and relied largely on centralized and other alternative monitoring methods, have been relied on by regulators and practitioners.
The Future

With the advent of EDC and other electronic systems, it seems “silly” to spend a lot of money to require that clinical trial data be entered first on a piece of paper and then be transferred electronically to an EDC system, and

If an electronic source documents could be created and few paper records be collected, it was agreed that there will only be a need to perform strategic monitoring of patient information not entered directly into an EDC system.
Proposition

Monitoring of clinical trials in the near future will involve a paradigm shift, so that rather than the monitoring of transcription errors, include greater emphasis on protocol compliance. For example:

- Documentation that the clinical sites are fully trained
- Monitoring of the drug and device supplies
- Assurance of compliance with informed consent
- Daily review of online data management reports
- Ongoing assessments of study metrics
Potential Barriers To Adoption

- The Risk-Averse Pharmaceutical Industry
- HIPAA
- EHR Industry
- 21 CFR Part 11 (FDA)
Results From a Direct Data Entry Clinical Trial

1. Screening error picked up early
2. Real time monitoring at the time of data entry
3. No need to do additional subject recruitment
4. EDC edit checks modified early in the game
5. Compliance issues identified in real time
6. Transparency of safety issues
7. Site saved 70 hours of data entry time
8. Major reduction in onsite monitoring
EDC
Live Demo
CONTACT

Jules T. Mitchel, MBA, Ph.D.

President
Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

212-681-2100 ext. 0
JulesMitchel@targethealth.com
www.targethealth.com