



.CRF

Electronic Data Capture and Workflow System for Clinical Trials

Business challenge

Most research takes place in different centers simultaneously. These are often located in different cities or even in different countries. It is required to prepare and distribute/dispatch all the materials - protocols, forms, etc to all the centers. Later, it is required to gather all the forms, ensure that the data is valid and prepare the data for statistical analysis. As it sounds, this process seems rather simple and straightforward.

Experts in the field of clinical trials know that it is not as simple as it sounds. The situation can become more complex if some data is missing or is not provided in appropriate form, if numerical values are out of range, if data are inconsistent, etc.

Many of those problems can be solved with IT solutions for clinical trials and the rest can significantly benefit from it. There are two approaches in providing IT solution for clinical trials - classic application and Web based solution.

Classic approach to IT support for Clinical Trials

Classic application, almost 100% of them Microsoft Windows based, is an out-of-the-box solution that needs to be installed on every computer that will be used in the process of collecting the data. Users simply install the application from the CD and start working. This is how it would be described in the advertising materials of such application, but in reality there could be many problems.

Levels of computer skills are different from person to person. So, some of them might require assistance while installing the software.

Many computers that are present in centers might not meet the minimal hardware requirements. IT security policies in clinics might be an issue for the installation of software. On the other hand, we still have the issue of dispatching - not the papers but the application!

Web based application

A Web based solution is the other approach. It does not require installation of any kind of software - only a web browser is required. All computers running Microsoft Windows have web browser readily available. For all other computers, it is very likely that it is already installed and if not, it's available free of charge. The application and the database reside on the central application server. All the users access the central server. This actually means that any computer connected to the Internet can be used for data entry.

One of the key benefits is that the maintenance of the application and the database is centralized. Data backup, security management, virus protection and operating system upgrades can be handled by trained personnel at one centralized location only. It is not required to distribute neither software nor paper materials - sending the URL of the application is all that is required. Users are not required to have any specific computer skills aside from knowing how to use Internet.

❖ A system with full data integrity and privacy of patients

❖ Standard web user interface

Solution

.CRF is a user-friendly, scalable and secure web application that has all the characteristics mentioned above. It runs from any standard web browser and offers many advantages compared to traditional methods of gathering data via paper forms or classic applications.

Data is entered at the source, in clinics. This way it is possible to avoid or at least to reduce the number of queries to the centers at later stages and most of issues regarding the validity and integrity of data are solved at the source.

Data entry forms

The user interface is standardized and intuitive across all data forms. The data entry system is both quick and easy to use. It supports a silent “heads down” entry mode or “heads up” mode where data entry operators are notified of all system generated discrepancies.

The system supports “single entry” mode of data entry, while the “double entry” with or without verification is an option.

Data entry forms are available from the patient's page which contains basic

information about the patient and links to data entry forms. The data entry forms have statuses to designate the stage of data entry:

- **Open** - data entry is in progress
- **Closed** - data entry finished, data is ready for verification
- **Answered** - in case query for that form was created and answered
- **Verified** - data is verified by data manager

Data monitor personnel can verify some of the forms while data entry personnel are still entering the data on other forms. This can significantly reduce the time to database lock.

Patient Data

Patient data		CD4 guided ARM		Logs	
ID:	16482	Visits	CD4+ cells	Status	
Patient initials:	TST	Week 0 (Pre-randomisation)			Trial Medication Log
Date of birth:	29.03.1960	Week 8 (Pre-randomisation)			Concomitant Medication Form
Baseline date:	24.10.2003	Week 16 (Pre-randomisation)			HIV Related Events
ARM:	2 - CD4 Guided	Week 24 (Pre-randomisation)			"Other" Adverse Events
Center:	(010) Zurich	Week 0	31%, 446	Verified	
Country:	(C-H) Switzerland	Week 1			
Screening Visit	Verified	Week 4	22%, 342	Verified	
Early Discontinuation Form		Week 8	18%, 299	Verified	
DISCONTINUED		Week 12	22%, 322	Verified	
Date:	15.07.2004	Week 24	25%, 270	Closed	
Reason:		Week 36	27%, 428	Closed	
6 - Patient's request		Week 48			
		Week 60			
		Week 72			
		Week 84			
		Visit before final			
		Final visit			
		Additional Pre-Randomisation Visit		Add	
		Additional Visit Type of Week 72		Add	
		Additional Visit Type of Week 84		Add	
		Optional Extra Visit		Add	
		CD4 Check Visit		Add	

❖ Full audit trail to track changes of the data

Solution

Data validation and verification

The main challenge with data entry is to ensure that the data is correct. To address this issue, a validation system is implemented. It warns the user if the data is different from what is expected. All warnings are displayed at the top of the form in the warning summary. Each warning listed in the summary is also repeated next to the value it validates helping the user to quickly find the possible problems on the form.

If a value a form is outside its expected or required range, the user can still save

the data and the warning will appear next time the form is accessed. The ranges and fields on forms are determined in the initial phase of clinical trial. If the value is missing or it is suspicious, the data manager can create a query while monitoring the data and assign it to the person that is responsible for providing the information.

The process of issuing queries is established as a part of the verification workflow between data entry and data manager personnel and finishes with the verification of the form.

When the form is verified, users cannot

modify the data anymore. After all forms are verified the process of data entry and verification is finished. Additional processing of data that might require expert validation is enabled (MedRA or WHO coding).

Staccato - visit week 24 - Microsoft Internet Explorer

Address: <https://staging.utils.biz/crf/forms/CD4Guided/week24.aspx?guidPatient=15a7e870-093e-44a9-b3c4-50268c916fe9>

.CRF Main Page | Patient Page | Data Management Current user: Admin Current date: 14.09.2004 Logout

Week 24

ARM 2 - CD4 Guided

Center: 010 - C-H

Patient ID: 16482

Patient Initials: TST

DOB (dd.mm.yyyy): 29.03.1960

Baseline date (dd.mm.yyyy): 24.10.2003

Please correct the following:

- Warning! CD4+ count is expected to be between 350 and 1800 /mm3!
- Warning! Glucose must be in range between 2.9 and 12.9 mmol/l
- Warning! HDL must be in range between 0.40 and 2.80 mmol/l

Date of visit (dd.mm.yyyy): 26.04.2004

Hemoglobin: 10.0 %

Platelets: 277 G/L (10⁹/L) ☐ ND

Biochemistry

Glucose <input type="text"/> mg/dl 13.7 mmol/l <input type="checkbox"/> ND	Total Bilirubin <input type="text"/> mg/dl 9.0 umol/l <input type="checkbox"/> ND
Cholesterol <input type="text"/> mg/dl 6.60 mmol/l <input type="checkbox"/> ND	Direct Bilirubin <input type="text"/> mg/dl 1.9 umol/l <input type="checkbox"/> ND
Triglycerides <input type="text"/> mg/dl 1.87 mmol/l <input type="checkbox"/> ND	ALT/SGPT 44 U/l <input type="checkbox"/> ND
HDL <input type="text"/> mg/dl 3.1 mmol/l <input type="checkbox"/> ND	LDL <input type="text"/> mg/dl 4.60 mmol/l <input type="checkbox"/> ND
Lipase 36 U/l <input type="checkbox"/> ND	Lactate <input type="text"/> mg/dl 1.4 mmol/l <input type="checkbox"/> ND
Amylase <input type="text"/> U/l <input checked="" type="checkbox"/> ND	Creatinine <input type="text"/> mg/dl <input type="text"/> umol/l <input checked="" type="checkbox"/> ND

Warning! Glucose must be in range between 2.9 and 12.9 mmol/l

Warning! HDL must be in range between 0.40 and 2.80 mmol/l

❖ **Complex validation rules**

- ❖ Various data exports to other data analysis applications
- ❖ Workflow implementation

Solution

Security and system administration

Security is implemented as combination of username/password and roles assigned to the users. Users could be assigned to a specific center or country and they can access only the data that belongs to that center. In fact, they may not even know that there are other centers or countries involved in the study.

Users of the system are placed in different categories depending on their role in the process of clinical trial. The system has 4 built-in roles:

- Data entry
- Data Manager
- Supervisor
- Sponsor

Data entry users only have permissions for entering the data. Data managers and Supervisors monitor the data entry. They can access and modify the data for all countries and all centers. They also have access to different reports that help them in their duties. Sponsors could access all the data but cannot modify any of it. For a given clinical trial, these roles can be modified and new roles can be added.

There are many other security procedures implemented at the application or system level of the solution. Users could be forced to change passwords at predefined intervals and a minimum length rule for passwords may be set. Security integration of the database with the underlying Operating System may be enforced. Access to the

data could be limited to a specific time of the day or a given period of time. Authentication can be implemented in more sophisticated way - i.e. using tokens or smartcards. Encryption ensures that the communication channel between the client (browser) and the application server is secure and data cannot be viewed or changed.

Technology and IT Support

.CRF is an enterprise-scale Web-based application which meets the demands of enterprise computing over an Internet standard distributed network infrastructure. The system can be accessed by any client capable of running a web browser. It has advantages such as:

- Centralized maintenance, administration and upgrading.
- Availability to all users regardless of their physical location.
- Reduced network traffic.
- Transaction mechanisms ensure data integrity and consistency in case of any system failure.

Solution is built using modern n-tier system architecture and is based on several industry standard platforms and technologies.

Business logic tier consist of:

- Microsoft Windows 2000/2003 Server
- Microsoft Internet Information Server
- Microsoft .Net Framework

The data tier is built primarily using Microsoft SQL Server 2000 (Oracle is also supported).

On the user side, the following client platforms are supported:

- Microsoft Windows NT 4.0/98/2000/XP, Mac, Linux
- Netscape Communicator 4.5 or newer
- Microsoft Internet Explorer 5.5 or newer

❖ **Advanced security built-in**

❖ **Centralized maintenance, administration and upgrading**

❖ **Framework customizable to specific clinical trial needs**

Conclusion

There are several approaches in developing a solution for clinical trials.

.CRF is a framework that is quickly customized into a solution for specific needs rather than requiring the clients/users/researchers to adapt to a solution and change the way they work. This way more flexibility is provided to our clients.

Behind the **.CRF** is a professional organization with highly educated employees ensuring continuity of the customization and development of the solution and understanding the needs of the users. This is especially important for small to medium sized companies that do not have their own IT department.





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