CLINICAL RESEARCH

Thérapie 2010 Juillet-Août; 65 (4): 317–322
DOI: 10.2515/therapie/2010045

Clinical Trials and E-Health: Impact of New Information Technology Applied to Clinical Trials (Including Source Data-Medical Records) and to Human and Drug Research

Jehan-Michel Béhier[1], *Jean-Charles Reynier*[2], *Pierre-Henri Bertoye*[3], *Muriel Vray*[4] *and participants of Round Table n°2 of Giens XXV*[⋆]

1 Laboratoires MSD-Chibret, Paris, France
2 Délégation Régionale à la Recherche Clinique et à l'Innovation, AP-HM, Marseille, France
3 Agence Française de Sécurité Sanitaire des Produits de Santé, Saint-Denis, France
4 Unité d'Épidémiologie des Maladies Émergentes, Institut Pasteur, Paris, France

Text received 4 march 2010; accepted 29 march 2010

Keywords:
e-health;
e-CRF;
e-diary;
clinical trials

Abstract – Within the last few years, new technology has come to play an important part in our professional and private daily environment. Healthcare has not escaped this progressive mutation with computers reaching the bedside. Clinical research has also shown growing interest in these new tools available to the clinical investigator, the patient, as well as to specialist departments for diagnosis and follow-up of patients, and to the different professions in clinical research. If the use of new technology seems to make life easier, by centralizing data or by simplifying data-sharing between different teams, it is still a matter of private data which must remain reliable, confidential and secure, whether it is being used in ordinary healthcare or in academic or industrial research.

The aim of the round table was to estimate the impact of new information technology applied to clinical trials (including source data-medical records) and to human and drug research. First, an inventory was made of the development of these new technologies in the healthcare system. The second point developed was identification of expected benefits in order to issue guidelines for their good use and hazard warnings in clinical trials. Finally, the impact of these new technologies on the investigator as well as the project manager was analysed.

1. From source document to database: inventory and courses of thought

1.1. Source data and medical records

A patient's medical record is a key element in clinical research. Indeed, the medical record contains all the patient's medical history which has to be consulted before his/her participation in a trial, as well as during and following the trial. In clinical research, documents in this medical record are known as "source documents",[1] containing "source data".[2]

Previously a patient's medical record was on paper, assembling clinical data and results from paraclinical exams. It identified the different healthcare professionals throughout the patient's life, by means of letters, notes taken in surgery and test results. Some records were incomplete or even difficult to interpret given the complexity of the patient's medical history; others were reduced to a strict minimum, or even lost in archives or medical departments.

Nowadays, thanks to new technology, a patient's medical record can be a computer file (or group of files) [Electronic Medical Record or EMR], centralizing all the medical data, from the clinical description to different paraclinical test results. The undeniable advantage of this new format is that it allows easier

⋆ For a list of participants, see end of article.

data-sharing between healthcare professionals, thus avoiding having to interpret illegible data and even to repeat tests. It simplifies filing, and is currently easier and quicker to consult being immediately available.

However, to make this data sharing efficient for the patient and the user (doctors, nurses, consultants, ...) as well as being technically competent, this data must have a consistent structure, naming conventions, in short obey rules and regulations adopted by all: standardization (*e.g.* HL7 in the United States)[3] allows interoperability between the different data systems.

Furthermore, for the patient and the people consulting this data (healthcare professionals or authorized clinical trial employees), the reliability and traceability of the medical data in the computer file is essential, whilst also respecting the integrity and confidentiality of this data.

In a clinical trial, a patient's data is collected from his/her medical record and copied onto a Case Report Form (CRF). With a classical "paper" medical record, relevant data for the clinical trial was compiled in a data report on the CRF. The Clinical Research Associate (CRA) checked that the data from the medical form and those on the CRF were coherent and corrected miscellaneous or missing data overlooked by the Clinical Investigator.

For the moment, this data verification process unfortunately remains the same with the electronic medical form.

Nowadays, the traceability and reliability of data on a patient's electronic medical record are still not complete through lack of standardization in the data recording process, a lack of traceability concerning modifications of this data and thus its interpretation, and to the general inability to guarantee its stability and integrity in the computer system hosting it (audit trail). This has two potential consequences:

- Printing off the source data needed to monitor the clinical trial, the print being dated and signed by the investigator.
- Compelling the investigator (or person appointed by the investigator) to copy the patient's data on the CRF, electronic or paper, and having this copied data checked by the project manager's associate (CRA).

To summarize, even though computer files are well established in hospital departments or in private consultation (specialists or general practitioners), their use as a source document for clinical research is restricted, mainly due to a lack of standardization and insufficient safety concerning the reliability and life span of this data.

Nowadays four requirements have to be met in order to allow an electronic medical form to be considered as a source document:

- Adopting standards in the appellation and structure of data (computer structure, but also semantic structure, using for example MeDdRA).
- Setting up access and individual rights concerning writing and reading the computer file, according to professional profile (doctor, nurse, clinical trial technician, secretary,...).
- Having an audit trail: the computer system must record and identify all modifications, the person who made them, and the date they were made.
- Regular data saving and reliable data archives.

Following these terms and thanks to new technology, collecting a patient's data and copying it on the electronic CRF could be computerized and would no longer need an intermediate paper stage. This data transfer must, however, follow a valid protocol for specific data transfer from the medical record to the electronic CRF.

1.2. Patient files and patient databases

Another major advantage in replacing paper medical records with electronic files, is that it gives a doctor wishing to carry out clinical research, access to a database made up of the entire clinical and paraclinical observations of his/her patients.

Providing minimal standardization (for example adopting HL7/CDISC rules and generalized use of dictionaries such as MeDdRA) in recording patient information during consultation or hospitalisation, the doctor or a member of his/her team could, at any moment and quite simply, query this database to identify patients eligible for specific research, whether epidemiologic or therapeutic.

To this day, however, a lack of standardization, homogenisation, compatibility and interoperability still persists amongst the different patient database systems for healthcare professionals set up in town or in hospital.

Furthermore, we have observed a redundancy in databases with no possible interface between them, especially in hospitals [pharmaceutic electronic patient file, PMSI (Informatic system for case mix)], other databases from laboratories or medical imaging departments...

Provided that legal requirements are respected, more precisely preliminary procedures for the French data privacy committee (CNIL), and that the people concerned are informed, technical progress should allow fusion of these databases thus limiting data redundancy. Interconnection of these databases would allow exhaustive data access to clinical research teams, thus increasing precision in finding eligible patients' profiles for a given research project (patient pool).

It is now necessary to develop standardized bases (with the electronic architecture of a database) including a tracking system (audit trail) of all entries and modifications of clinical and paraclinical data. To accomplish this ambitious aim, the users must

first define their needs for this equipment (use, type of query, ...), an exhaustive list of data to be recorded and information from other departments to be integrated (biology, imaging, ...), then establish on this base either open or specific standards, if the open standards do not cover specificity of data. Developing this type of base requires defining functional specifications, using risk analysis and having the software technically validated. A panel of tests performed by different users complete database testing before its production.

Technology and computer software quite easily meet the users needs, however, it must be noted that a lack of human means or logistics, hinders the set-up and management of this new equipment.

Another critical point (resulting from risk analysis) is user training and ensuring that this training is fully understood.

1.3. The electronic-Case Report Form (e-CRF) and study database

Establishing an electronic-Case Report Form (e-CRF) for clinical trials has substantially changed cooperation between the different partners in clinical research.

Firstly, from a human point of view, dialogue between the CRA and clinical investigator previously only revolved around the patient during the concordance checks carried out on-site by the CRA, but is now replaced with discussions on how to fill in the e-CRF and dealing with electronically sent questions or "queries" (see below), as well as discussing the technical problems encountered. Furthermore, the e-CRF has created a new job, data capture management, under the supervision of the investigator. Checking data consistency is now carried out *via* "queries" on the e-CRF itself, warnings using different alert signals indicate erroneous, incoherent or missing data. Some of these queries are automatically generated (in the case of simple incoherence such as age or weight), or more commonly nowadays, come from fact checking data.

This "query" mechanism is linked to an "audit trail" and thus to meticulous traceability of any subsequent modification of data on the e-CRF.

In addition, development and use of the e-CRF in clinical trials are evidently a breakthrough, making carrying out clinical trials easier, especially concerning the real-time availability of clinical data.

For the investigator, apart from the reduce in sheer volume (bulky patients' files close at hand throughout the trial), the immediate advantage is simplified data management with automatic checks, reducing the number of queries or DNF, and easy data access with simplified saving and archives.

For the Sponsor, the main advantage is the time saved in data management (no redundant data capture, taking away the difficulty of reading sometimes illegible handwriting, real-time collection and access to data, on-line data encryption, traceability of data correction, direct downloading of biology data or other centralized paraclinical tests, ...). It allows the Sponsor to access real-time a list of unwanted side effects during the trial and therefore to immediately informs the Health Authorities, as legally required by the Public Health Code.[4]

If both national and international multiple site studies can obviously profit from e-CRF, above all for its easy data management, simplification and optimization of monitoring, due to direct and real-time access to patients' data, necessary for quality control by CRAs, the expected benefits may seem less crucial to a simple site study.

Effectively, the use of e-CRF may seem less evident in a simple site study, especially at first sight if we compare putting together a simple paper case report form with setting up a computer interface demanding specific technical skills. Nevertheless, when we consider the chain of people involved in data management, analysis and use, the e-CRF and its data traceability should vouch for higher quality compared to a paper form with an Excel spreadsheet. The advantages gained may surpass the research study itself, making data aggregation between studies easier (respecting prior legal declarations). Reducing or getting rid of paper forms would make filing and storage easier, whilst making data transmission more dynamic.

In addition, reliability, traceability and authentication of data is guaranteed electronically through standardized procedures and tools, using nominal access, electronic signature but also the audit trail, which identifies interventions in the database and those responsible for them. Moreover, once established, the e-CRF and database get regular maintenance updates.

Therefore a computer system actually guarantees the quality of data and so ensures better care of the patient.

Of course, using the e-CRF requires human and material resources and supplementary technical skills. For academic and institutional research which lack financial and technical means, it would be best to support initiatives promoting easy-to-use databases, with validated user processes (audit trail, maintenance, filing) and standardized data capture, easily adapted to a type of research. Prior to creating a database for a study, decisions have to be made concerning the data to collect (interest and use), as well as the concordance checks necessary. Right from the conception of the e-CRF there must be coordination between the clinical investigator, the person responsible for filling in the e-CRF and the computer scientists

Nowadays, even though e-CRF have become common practice in multiple site studies, there are users, investigators or CRA,

who remain reluctant to use this new equipment. It has been shown that there are real advantages especially concerning availability, follow-up, data corrections and exchange of information.

To overcome reluctance on behalf of protagonists in clinical research, several courses of thought can be suggested, all based on formalisation of the processes, methods and work tools shared by everyone concerned:

- Offer the users training, presenting both the interests and advantages of this new equipment, whilst reminding them of legal requirements and their responsibilities, as well as the way it must be used (confidentiality, respecting private codes and passwords, CNIL registration at set up of new information systems, ...). This training must also supply details on how to fill in the different parts of the e-CRF.
- Acknowledgement of new jobs in clinical research, as well as their skills as well as providing information and deciding on different levels of commission and intervention concerning the database. Harmonize methods used.
- Develop acknowledgement of e-training, e-learning and certifications for given software.

1.4. The e-diary

A patient's paper diary from a clinical trial is often very difficult to make use of, due to uncertainty of the patient noting data, particularly over time (traceability, accuracy in the time schedule and in noted data), it being impossible to ask the patient about illegible or incoherent data afterwards, whereas information given directly by the patient could be very useful.

An electronic diary is used more and more often in clinical trials. Its aim is to improve the quality of information collected from the beginning and throughout the trial, using programmed alarms (reminder to fill in questionnaires) and with the patient receiving educational help from the investigator.

Moreover, to a certain extent the investigator ensures the accuracy of the information (access code for the patient, direct download of information into the trial database). In some cases he/she can have real-time access to the information typed by the patient on a website, and if need be contact them if they forget.

Use of an e-diary does have its limits: for example, the patient's capacity to understand an investigator's explanations or those related to his/her pathology.

Setting up this sort of equipment implies that the personnel in charge of research is trained to use it and is capable of explaining how to use this electronic monitoring diary to a patient. The investigator must also have the means to measure the patient's observance, particularly when the main criteria for assessment of the trial is based on on this data.

Yet again, this requires a genuine effort of explaining to each protagonist how the e-diary fits into the clinical chain, what it brings for example to the care of each patient, and therefore an unusual effort to formalize the overall process.

1.5. Electronic data transfer

Two situations in data or document transfer were discussed.

1.5.1. Data transfer between the Sponsor and Health Authorities

For clinical trials in France, data or document transfer between the sponsor and the health authorities must be discussed. The unanimous, favourable report following the positive experience with the French Medicines Agency (Afssaps) and regulatory filling concerning transferring data or documents leads us to recommend harmonisation of transmission procedures, especially between the "Comité de Protection des Personnes" (Ethic Review Committee) and the Afssaps. The round table therefore strongly recommends developing a common exchange format, guaranteeing data confidentiality, such as Eudralink at first, followed by a standardization of exchanged data and information, drawing for example from the HL7/CDISC[3,5] recommendations.

1.5.2. Data or database transfer between investigator, sponsor and service providers

Data or database transfer between the investigator, sponsor and service providers may seem evident given that information is exchanged frequently and without real limits, especially technical. Legal requirements concerning handling private data demand accurate identification of the categories of recipients of this data in a file submitted to the "CNIL" and Data processing regulatory agencies (CCTIRS) [or, if applicable to the given study, in accordance with the Reference Methodology MR 001], laying down security measures ensures confidentiality whilst at the same time respecting legal data transfer supervision plan within Europe (freedom of data movement) and outside Europe (SAFE HARBOR, transborder flux conventions or Binding Corporate Rules): it is important to note that this transfer would be under the sponsor's responsibility in any case. Transferred data may not be used in anything other than research (intended use submitted in the demand to the CNIL, or if applicable to the given study, in accordance with the reference methodology MR 001).

It is important to check the integrity of the data after every exchange as well as the global safety of the transmission system.

It is strongly recommended to develop a standardised and safe exchange format such as CDISC, and to adopt it as statutory format within the European Union.

Along the same lines as this recommendation, it is important that contracts between participants clearly stipulate format, storage and data exchange protocols that can also be audited.

As for pre-existing clinical trial databases, there are no further recommendations than these. However, this easy data access which allows decisions to be made quicker, especially within the Data and Safety Monitoring Board (DSMB), must be in accordance with Good Clinical Practice. Indeed, the risk of interpreting results (illegal, hidden analysis) from data whether aggregate or not, must be under complete control, and "masked" data and randomisation decrypting files must be able to be proved completely separate.

In the same way, ethical issues must not be treated differently because the data is compiled electronically and not on paper, both must mention legal requirements of confidentiality and information, and where stipulated by law, include personal consent of those involved.

An effort must be made concerning anonymity and encrypting paraclinical documents (imaging CD, biological data, ...) to develop software adapted to the needs of everyday healthcare and research.

2. Recommendations and key points

New information technology applied to clinical trials has uncontested advantages in research project management, being easy to use, as well as making results available more quickly and therefore accelerating patient care. Nevertheless it is important for the designers and the users to take into account the users rules for this new technology. Indeed, concerning either clinical research or collecting health data for a patient, it is essential to ensure comprehension (standards), reliability, traceability and confidentiality of this data, whilst respecting legal requirements and safety regulations.

2.1. Patient source document/medical record

- Standardization of codification and structure of data/informations.
- Development and use of safe software and databases which have an audit trail.
- Individual access and private passwords.
- User training and training material.
- Systematic saving and reliable filing.

2.2. e-CRF – e-Diary

- Formalisation of procedures and rights and duties of all the participants, including responsibility for producing and using data, but also how their production and use affect the final outcome of the research project and patient care.
- Give users a sense of responsibility (private access, information on roles and commissions).
- Acknowledgement of e-training for given software.
- Reminder of obligations in data protection: submission to the CNIL at the time of software set up, rights information (access, ...) and duties (confidentiality, ...)

2.3. Data transfer

- Recommendation of a safe common exchange space, such as Eudralink, for exchanges with authorities (Afssaps and CPP).
- Development of a safe and standard common exchange format such as CDISC, adopted as statutory format within the European Union, in order to guarantee data safety throughout the clinical study to avoid any illegal or hidden analysis.

2.4. Clinical study databases

- New information technology Is of no impact since it makes data available real-time.

2.5. Ethical aspects

- Same legal settings as for paper-"Loi informatique Fichiers et Libertés" (Data privacy law).
- Obligation to show legal requirements for confidentiality and information:
  - to the patient (with their consent if legally required), and to all research administrators.
  - to be adapted to the type of media.
- Recommendation: encourage the development of tools ensuring anonymity of electronic data (imaging CD or laboratory results).

Several of these points are currently being discussed in work groups and should soon lead to the publication of recommendations for data management, traceability and safety.

2.6. An non discussed supplementary subject

All the elements discussed above contribute to collecting material concerning clinical research of all kinds.

This material, nowadays predominantly electronic, is used in several ways:

- Transmitted to higher authorities, during and following clinical research.
- To argue a release for market access or a transparency file.
- To follow unwanted side effects and pay sufficient attention first to the patient then to the authorities.
- To add to the reference data in the "Trial Master File".

At the next Giens meeting it would be interesting to discuss the limit between data collection and documentation, as well as management of the latter.

3. Conclusions

New technology now plays an important part in health as in human and drug research clinical trials. Its use has changed some habits and practices. It includes some extremely well structured and organised tools.

The Round Table strongly suggests discussing the importance of e-health among health protagonists, reminding them of the expected advantages of this new information technology, not only in clinical research (institutional, academic or industrial), but also from the point of view of medical responsibility: standardization and traceability of collected data improving quality, reliability and it's availability. This would also allow clinical research teams to be recognised as competitive protagonists, capable of identifying eligible patients for a clinical research project, thus improving the predictability of their enlistment. It also increases the speed of data availability allowing quicker decisions, especially for the DSMB. This easy access must however, respect Good Clinical Practice and legal requirements concerning personal data processing. New technology is unmistakably a major issue in clinical research, but it can only be efficient and operational if accompanied by sufficient human and logistic means.

Participants. Béatrice Barraud (Inserm, Paris), Jehan-Michel Béhier (Laboratoire Merck Sharp Dohme-Chibret), Pierre-Henri Bertoye (Afssaps, Saint-Denis), Nathalie Beslay (Avocate, Paris), Julie Boussuge (CHU, Bordeaux), Loïc Chartier (Institut Pasteur, Paris), Erick Gaussens (Laboratoire Product Life), Marta Gersberg (Laboratoire Sanofi-Aventis), Eric Leutenegger (Laboratoire ABR Pharma), Monique Malchiodi (Laboratoire Roche), Dominique Menuet (Laboratoire Pfizer), Noureddine Namir (Laboratoire GlaxoSmithKline), Jean-Charles Reynier (AP-HM, Marseille), François Rivaille (Laboratoire Servier), Stéphanie Sallman (Afssaps, Saint-Denis), Marie Sebille (Laboratoire Sanofi-Aventis), Gilles Sonou (Peter Holmes), Muriel Vray (Inserm/Institut Pasteur, Paris)

References

1. Décision du 24 novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur les médicaments à usage humain. Glossaire, définition 1.17. http://www.legifrance.gouv.fr
2. Décision du 24 novembre 2006 fixant les règles de bonnes pratiques cliniques pour les recherches biomédicales portant sur les médicaments à usage humain. Glossaire, définition 1.18. http://www.legifrance.gouv.fr
3. www.hl7.org
4. Décret n° 2006-477 du 26 avril 2006 modifiant le chapitre 1er du titre II du livre Ier de la première partie du Code de la Santé Publique relatif aux recherches biomédicales. Art. R.1123-44. http://www.legifrance.gouv.fr
5. http://www.cdisc.org

Correspondence and offprints: *Jean-Charles Reynier*, Délégation Régionale à la Recherche Clinique et à l'Innovation, AP-HM, CHRU de Marseille, 13354 Marseille Cedex 05, France.
E-mail: JCREYNIER@ap-hm.fr