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Is WorkFlow technology suitable to represent and manage clinical trials?

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Abstract:
The clinical trial has to be rigidly followed because it identifies a uniform clinical behaviour, which has to be adopted by the different physicians carrying out the test. The life cycle of the clinical trial is therefore based on a planning and definition phase, a next experimental phase connected with its diffusion to the involved centres and finally an evaluation phase of the results. An information system, which supports the users in the different phases of the clinical trial life cycle, has to take into account the different characteristics of each phase. The aim of this paper is to illustrate the role of WF technology as a component of an information system which supports the life cycle of a clinical trial also on the basis of the experience of the Italian Group for Haematological Disease of Adults (GIMEMA).

1. Introduction

A patient treatment is based on clinical procedures, which have the agreement of specific medical schools and associations as well as the acknowledgement of governmental health care committees. The acknowledgement of a new therapeutic and/or clinical procedure is obtained through the evaluation of one or more clinical trials carried out in collaboration with different health care structures and tested on a meaningful number of patients opportunely selected. The involved structure may be spatially distributed.

The clinical trial has to be rigidly followed because it identifies a uniform clinical behaviour, which has to be adopted by the different physicians carrying out the test. Only in this way the effectiveness of the a new drug or of a new procedure can be evaluated because the rigidity of the execution represents one of the elements which guarantees homogenous data collection as well as a correct analysis of the results. Moreover, in Italy the testing procedures used to evaluate new drugs on human beings are very strict being ruled by a Ministry Decree [1]. This norm, in keeping with the European legislation, assigns rules of "good medical practice" which binds the behaviour of each one taking part in the test [2, 3, 4]. The life cycle of the clinical trial is therefore based on a planning and definition phase (which includes both scientific and administrative activities such as the approval of the ethic committee), a next experimental phase connected with its diffusion to the involved centres, and finally an evaluation phase of the results. An information system (IS) which supports the users in the different phases of the clinical trial life cycle has to take into account the different characteristics of each phase. In the planning and definition phase it is necessary to describe, in a very detailed way, the clinical trial to be applied to a patient with specific characteristics; in the experimental phase the clinical trial has to be instanciated and executed in relation to each patient of the different structures taking parts to the test; finally in the evaluation phase it is necessary to analyse statistically the data set of the instanciated clinical trial. In all these phases workflows (WFs) play an important role as methods of process representation as well as technology for their static and dynamic management.

A WF is the "automation of a business process, in whole or part, during which documents, information or tasks are passed from one participant to another for action, according to a set of procedural rules" [5]. The use of a WF implies a formal representation of a process, in our case a clinical trial, in terms of tasks, actors, documents, etc. A WFMS is "a system that defines, creates and manages the execution of workflows through the use of software, running on one or more workflow engines, which is able to interpret the process definition, interact with workflow participants and, where required, invoke the use of IT tools and applications" [5]. The use of a WFMS makes it possible to define and then manage processes. For this reason WF technology applied on clinical trials improves: a) process standardisation, b) process management, c) efficient delivery of information-based tasks to workers, d) explicit focus on process design.

The aim of this paper is to illustrate the role of WF technology as a component of an IS which supports the life cycle of a clinical trial also on the basis of the experience of the Italian Group for Haematological Disease of Adults (GIMEMA).

2. The life cycle of a clinical trial

Each phase of the clinical trial has its own objective, different users, specific activities to carry out as well as different roles played by the use of both WFMSs and networks (tab. 1).

Definition of the clinical trial - In order to introduce into the clinical practice a new drug or a new procedure, it is necessary to test its validity. To this end a group of physicians, experts of the field, write the clinical trial following standardised criteria expressed by the rules of good medical practice. To obtain the approval of the test, the clinical trial has to be described according to a defined set of information, such as premises and scientific and ethical motivations of the study, requirements of the experimental centres, treatment planning, statistic method of evaluation and scientific bibliography. The definition of the clinical trial is a complex activity, which implies recurring analysis and discussions; it is subjected to several updated versions by the writing committee, which has to define the clinical trial in a co-operative way. For this reason fundamental roles are played by the WFMS (supporting the formal description according to pre-defined schema, which are coherent with the procedures of the co-operating group and with the rules of good medical practice) as well as by networks (supporting the communication among the members of the writing committee in the co-authoring of the clinical trial.

Testing and diffusion - To have a successful result of the experimental phase, each instance of the test activity need to follow exactly the clinical trial in terms of both clinical activities, and data collection. The possible variations of the clinical trial, which may occur during this phase, have to be recorded and justified. Another parameter which influences the test is the number of centres and of clinical cases chosen to carry out the test. For this reason in this phase there are different users, each one with his/her own objectives, which make them access the information of the clinical trial according to different views. For example the physicians, who are testing the clinical trial, need information to execute it correctly, to be abreast of the possible modifications, to exchange information with other centres and to collect data in a centralised way. For these reasons fundamental roles are played by the WFMS (used as a tool to control the execution of the different instances) as well as by Intranet (used as a channel to communicate the information). The physicians, who "navigate" on the web, are interested to get information on current clinical trials and to know the necessary requirements for their possible participation. The patients, who are today getting more and more aware of the available different treatments, represents another type of users, interested to know benefits and risks of new drugs and/or treatment procedures. For these reasons fundamental roles are played by the WFMS (used as a tool to

describe the clinical trial according to different views) as well as by Internet (as a channel for the diffusion of information).

Table 1 – The life cycle of a clinical trial

	Definition of the clinical trial	**Test & diffusion**	**Evaluation & analysis**
OBJECTIVES	• identification and definition of a new diagnostic or therapeutic procedure to test	• test of the new procedure on an adequate number of patients in different structures	• evaluation of the clinical trial • diffusion of the test results
USERS	• physicians of the writing committee • sponsor of the clinical trial • Data Centre	• testing physicians • *navigator* physicians • patients	• researcher physicians • testing physicians • patients
CENTRAL ACTIVITY	• description of the clinical trial	• Uniform execution of the instanciated clinical trial	• analysis of the new data and information resulting from the test
ROLE of the WFMS	• supporting the formal definition of the clinical trial in terms of activities, resources, etc., and according to the procedure of the co-operative group and to the norms of good medical practice • supporting the analysis of the model of the clinical trial	• instanciating the clinical trial for each patient • execution of the automated activities • guide/control of the execution of the manual activities • guide/control of the data collection related to the execution of each test	• supporting the statistic analysis of the tests
ROLE of the NETWORKS	• supporting the communication activity for the co-authoring of the clinical trial	• availability of the information necessary to test the clinical trial • diffusion of the information on the clinical trial to a wider range of users	• diffusion of the results of the test
ADDED VALUE of the AUTOMATION	• formal and integrated description of the clinical trial	• comparison of tests	• wide diffusion of the results

Evaluation and approval. In this phase it is necessary to evaluate the results of the clinical trial according to the statistical analysis techniques chosen during the definition phase. If the tested hypothesis is confirmed, new guidelines are going to be used in the current clinical practice. Also the evaluation of the clinical trial is a complex activity, which implies different steps for the analysis of data and discussions among physicians; it is therefore based on the participation of different users, each one with specific competencies and roles (data manager, bio-statisticians and physicians). For these reasons fundamental roles are played by the WFMS (as a tool to evaluate the clinical trial), by Intranet (as a channel to communicate the information among the testing team) as well as by Internet (as a channel to the diffusion of the results of the test).

The added value given by the automation is: a) the formal description of the clinical trial based on the WF conceptual model; and b) the enactment and evaluation of WF instances based on the use of WFMS. In table 1 we have considered only the advantages of using WFMS, and we have not mentioned the advantages which can derive from the use of other software such as datawarehouse or application packages for data analysis, which can be linked to WF systems to enhance the evaluation and approval phase.

3. The information model

The conceptual model of a clinical trial described by the UML model is shown in fig. 1.

The attributes of a clinical trial are: the title, the type of clinical trial and different dates (definition, updating), etc. A clinical trial is also described in terms of: a) target population; b) criteria for the inclusion (the eligibility of a patient) or exclusion; c) its aims (main and second); d) the events that may occur in the enactment of a trial; e) the description of the drug, result of this trial.

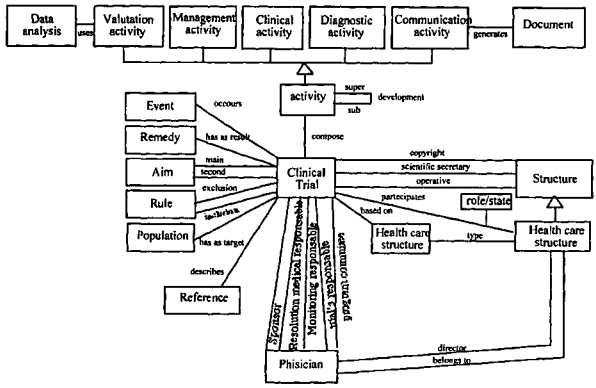

Fig. 1 – The information model

The clinical trial is composed by different activities (composed by activities): evaluation activity (that uses particular data analysis methodology), management activity, clinical activity, diagnostic activity, communication activity (based on pre-defined documents and formats). The clinical trial needs healthcare structure types and uses healthcare structures according to type, role and state (active participation, scheduled participation, etc.). In general a structure executes the task of the management secretary, or of the scientific secretary; a structure has the copyright of the clinical trial. The physicians belong to a healthcare structure and only one may manage it. A physician has different role related to a clinical trial: component of the Program Committee; scientific manager, monitoring manager, or clinical decision manager; sponsor of the project. The attributes of the physicians and structures are: name, address, phone number, e-mail, etc.

4. Clinical trial management: the GIMEMA experience

GIMEMA involves more than 70 Italian centres, participating into studies mainly for acute leukaemia. It joins EORTC (European Organisation for Research and Treatment of Cancer) Leukaemia Group for several international co-operative clinical trials. GIMEMA operates throughout a central Data Centre in Rome, which is in charge for: 1) preparing/reviewing protocols and case record forms (CRFs); 2) collecting, entering and analysing data; and 3) co-operating with researcher physicians for scientific reports writing. GIMEMA manages several protocols active at the same time and tries to register all acute leukaemia cases – including cases not eligible for any protocol – to realise a kind of national register of acute leukaemia, to have data on the ratio of eligible population above the total population referred to a given centre with a given disease. Thanks to a grant of the Italian Association against Leukaemia, in 1998 GIMEMA started to build up an IS, including a partial automatic data flow control and data check.

The main goal was the implementation of a system which enables the participating centres to evaluate the patients' eligibility automatically. The system based on Lotus Notes [6] allows each centre to work locally using the common GIMEMA procedures and to update periodically the general database. The main system functionalities are: (1) to collect data from centers through Internet, (2) to check data at the time of data entry, and (3) to guide the user/researcher throughout the protocol proposing the correct CRF at the correct time (as an example, if a patient die in induction treatment, the consolidation form is skipped and the system ask for the off protocol form).

The following architecture has been to implemented by now:

1) **Strata 1: Registration and eligibility**: a Registration form register basic data of the patients, with all variables needed to evaluate his/her eligibility for any GIMEMA protocol. After the form is filled in, the automatic evaluation "mails" the form of eligible patients for a given protocol to the protocol database; forms of not eligible cases remain in the registration database.

2) **Strata 2: Treatment Protocols:** a database for each protocol is present, with all the CRF for any protocol. The first form of any patient in each protocol is the "copy" of the registration form, that has been "mailed" from the registration data-base (see above). Starting from this first form, a software-guided flow proposes the next form for the correct data entry. An automatic follow up form (including date of last follow up and status) is produced as soon as a form is completed.

5. Conclusion and future work

The use of WFMSs facilitates co-operation and communication activities and data exchange in the execution and evaluation of the clinical trial. WFMSs answer the need of co-operation and co-ordination of designing activity and monitoring clinical trial. Moreover the structures involved in the clinical trial are spatially distributed and consequently we have to adopt a distributed approach in order to facilitate communication, sharing of data sets and procedures.

According to the life cycle described in this paper, the system supports the evaluation and analysis phase of 7 clinical trials with 20 connected centres. Concerning the test and diffusion phase the system guides the enactment of an activity instance and proposes the correct CRF whose data are then stored in a database via Internet.

A collaboration between GIMEMA and CNR aims to improve the IS adding further functionality of WFMS such as the guide/control of the execution of the entire manual and automatic process. At the moment we are working on the development of a system supporting the definition phase and in particular the co-authoring of a clinical trial based on Atreus workflow model [6]. A further important development step is to deliver the final and/or updated version with the all possible amendments of each clinical trial to the participating centres. This requires functionalities, which improve the co-operation, communication and co-ordination among the GIMEMA centres.

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