SOP-Creator – A Tool for the Management of Standard Operating Procedures

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Abstract: Standard Operating Procedures (SOPs) are a significant element of quality assurance in health care. They consist of practical, mandatory instructions for frequently occurring tasks in the performance of clinical trials. The methods of how to accomplish these tasks embody the current state of medical knowledge and are approved by a consensus vote of domain experts. This paper shows the usefulness of a workflow-based web application for knowledge distribution in large research networks[1]. It analyses the needs for coordinated collaboration, describes conceptual aspects and discusses an approach to formalise SOPs.

1 Introduction

To compare the results of clinical trials, it is important that all stages are performed in the same high-quality manner. As a consequence of the 12th amendment of the AMG [Amg04] (German drug law), the performance of therapy optimisation trials[2] must comply with the standards of Good Clinical Practice [ICH96]. To ensure this, SOPs define mandatory procedures according to ethical and legal requirements. SOPs cover all aspects concerning the design, organisation, implementation, supervision, documentation and evaluation of clinical trials in study centres. Traditionally, SOPs are paper-based documents that are created, maintained and used by a team of people. Frequent problems include overwriting of files, missing control of changes and incorrect metadata and lead to detraction from application. Moreover, in decentralized research networks, authors and experts are widespread such that editing by means of standard text processing software and mail-based distribution have proved inappropriate.

[1] http://www.lymphome.de/en/Projects/SP02/SOP-Creator/

[2] The objective of therapy optimisation trials (TOT) compared to regulatory trials is to improve standard therapy treatment, for instance in cancer chemo therapy. TOTs use only approved drugs trying to find more effective dosages and combinations of drugs instead of exploring new pharmaceutical substances. In the past, legislative regulations for TOT quality assurance protocols were less severe.

There is thus a need for computer-assisted SOP management with distributed editing, central administration and workflow functionalities. Such a web application based on an existing content management framework has been developed within the competence network of malignant lymphoma, an association of 9 study groups and 13 sub projects.

2 Objectives

The primary aim for SOP development is to achieve und retain excellence: to continuously guarantee high quality of all processes in clinical trials, to provide a documentation of all actions taken that is subject to validation, to ensure the comparability of therapy measures in different trial centres, to minimize the number of errors and to lower the training time for new staff. To obtain such a level, a working group for quality management was founded to define adequate quality standards and develop computer-based tools to support this quality oriented strategy [Pfi03].

The basic goal was to provide a central computer-based quality management platform containing all SOPs and associated documents in their latest versions. It must not require any specific client-side software since that often becomes a problem in high security areas working with patient data. An appropriate SOP management tool would have to comply to the following concepts:

1. *Communication:* To ensure easy access for all users, an application based on WWW protocols was demanded. It should provide a comfortable way of viewing, editing and exchanging documents. Furthermore, it had to support functionalities like listing all personal tasks, automatically assigning and forwarding tasks, reminding of expired SOPs, dunning, validating standard compliance and investigating relevant experts.

2. *Collaboration:* One fundamental requirement was to provide 3 variable views for the 3 user roles: (1) an edit view for SOP authors showing the most current version of an SOP with all changes made at present, (2) a quality assurance view for domain experts including only those changes that were explicitly submitted for publication by the authors and (3) a released ready-to-use view as the main knowledge distribution channel for clinical staff.

3. *Verifiability:* Another objective was the verifiability of changes made in SOPs. Every version must have an unique version identifier. Since documentation is subject to validation, a journal must keep records of every modification for auditing purposes by logging user name, time, action and an optional remark.

4. *Workflow support*: A focal point was workflow support. As mentioned in [Sch01], workflow management systems are best suited to map and support routine processes. The life cycle of an SOP can be classified as a routine process according to Picot [PR95] since it satisfies the conditions for:

- Low *complexity*: Process structure is flat. Tasks are executed sequentially. The number of sub tasks, their interdependence as well as the number of user roles are limited.
- Low *mutability*: The SOP management workflow is an standardised process and process instances are unalterable.
- High *level of detail*: The SOP management process can easily be divided into sub tasks. Input, output and transformation steps of each sub tasks can be clearly defined.
- High *division of work*: A lot of people are involved in the creation of an SOP. Hence, there a strong need for coordination.
- Medium *interprocess linkage*: Since SOPs refer to the content of other SOPs, they may have dependencies, but the corresponding SOPs are known to the authors.

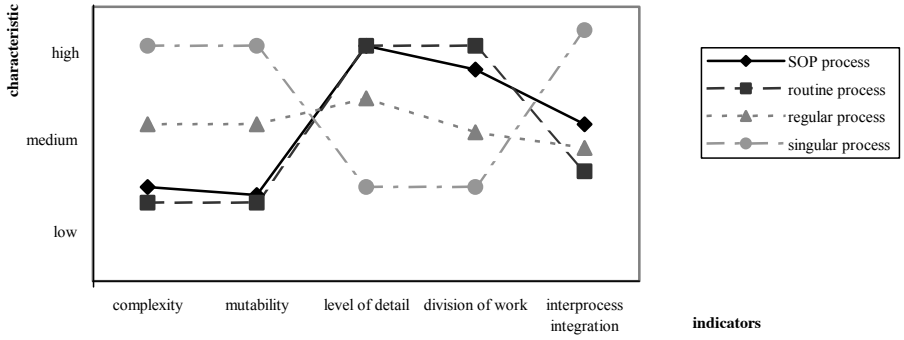

Figure 1: Characterisation of the SOP workflow model according to [PR95]

3 State of the Art

When a preliminary market analysis was made in 2001, it showed that existing software solutions for distributed editing of SOPs provided convenient editing, layout templates and multiple authors capabilities, however, they failed in collaborating over the Internet, running on different operating systems, managing SOP attachments and offering electronic reminding. Most of these problems are gone. In the last years, the market for quality assurance software has split up into 3 segments. The first segment continuous to focus on local PC or client-server installations in closed environments. These programs are not limited to SOPs in the medical domain, they can be deployed in chemical laboratories or manufacturing. They try to facilitate the quality assurance process entirely. This includes working instructions, checklists, process instruction, maintenance plan and more. Examples are mpm *SOP-Speed* or Chromasoft *SOP Manager*[3].

[3] http://www.sop-speed.de/ and http://www.chromasoft.de/pages/sop.htm

The second segment consists of tools that specialize in the management and distribution of SOPs within pharmaceutical companies and clinical/academic research organisations. In 1997, the US Federal Food and Drug Administration (FDA) forced regulations on the use of electronic records and signatures in computer systems within the Medical Device and Healthcare industries, entitled 21 CFR Part 11. An equivalent directive was published by the European Community in December 1999. Compliance to FDA 21 Part 11 have become ever since a vital issue. Most of these specialized tools are web-based thin clients, for instance Distinct Horizon *MxDoc*[4] or *Macrodome Docusop*[5].

The third segment combines existing enterprise document management systems with extended functionalities for regulated documents. Because of the cost and complexity of such an installation, the target group are large pharmaceutical companies that need a holistic approach which manages all regulated document types, supports a full document lifecycle workflow, maintains security and ensures FDA compliance. Examples for such services are OpenText *Livelink für Regulated Documents*[6] or Documentum *Compliance Manager*[7].

All of the programs mentioned above are commercial implementations. There are no widespread open source tools. With regard to the financial limitations in academic institutions like university hospitals and the need for distributed editing, the second option is most suited for research networks. The *SOP-Creator*, even it has no approved FDA validation, would fit into this category.

4 Implementation

4.1 SOP-Workflow (abbreviated overview)

If a member of the working group for quality management thinks that a certain SOP is missing, he makes a call to the group. At first, a survey is made to confirm the need of such an SOP. Then, a first draft is created. This draft is read, commented, modified and revised by other experienced SOP authors. This is the specialist's stage of intensive knowledge acquisition and exchange. When the primary author claims that the draft complies with the quality standard, he submits the SOP to the quality assurance stage. Now the draft is reviewed by external experts.

The board of experts must come to a consensus vote. This is called the expert's stage of knowledge acquisition. If the SOP contains mistakes, it will be rejected, thus responsibility is given back to the SOP authors. Otherwise, the SOP will be released by the board of trail coordinators and be declared as mandatory for routine operation.

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[4] http://www.distincthorizon.com/solutions/sopmanagement.html
[5] http://www.macrodome.com/macrodome.nsf/SOP?OpenForm
[6] http://opentext.com/pharmaceutical/livelink-for-regulated-documents.html
[7] http://www.documentum.com/solutions/compliance/dctm_compliance_manager.htm

4.2 SOP Structure

In contrast to paper-based SOPs, computer-managed ones clearly separate content from layout and metadata. Because of this separation, metadata can be accessed and used by external programs, boosting the potential field of application. An e-SOP consists of:

- its *hypertext content* – natural language marked up with mainly structural and logical HTML tags like headings, paragraphs, code samples or abbreviations
- a *layout template* for maintaining corporate identity, this enables design changes to be made only once but spanning all SOPs
- three sets of *metadata* – (1) a Dublin core like schema including title, author, keywords, (2) a repository specific schema providing target group, expiry dates, object state (f.i. "checked out" or "submitted to quality assurance") and (3) a self-defined metadata extension comprising of sop id, date of final release, textual description of the last changes and so on
- a set of *references and attachments* that link to corresponding SOPs or related documents that belong to a certain SOP
- a list of *principals and rights*. Users are ordered in groups according to their position within an organisation. Also, users belong to certain roles according to their functional area. Users, groups and roles are called principals. Each SOP has an access control list which stores all principals and their respective rights.
- a *versioning and audit trail*. Every time an SOP is changed, its version number increases. Old versions must be archived and restored on demand. The log journal can always show the appearance of an SOP at a certain date and time.

4.3 SOP Management Tool "SOP-Creator"

To fulfil the requirements mentioned in the previous chapter, a dedicated tool has been developed. The SOP-Creator is a software application based on the Content Management System (CMS) Gauss VIP. For the input, modification and verification of SOPs, a HTML client has been extended with SOP-specific expansions and a comprehensive metadata schema. The client offers a user-friendly interface for editors and quality assurers. Write locks for SOPs that are checked out for editing prohibit unintentional overwriting. The administration of SOPs takes place in the CMS and comprises a multi-stage quality assurance workflow, granular rights at object level and reference maintenance. User Management is provided by an LDAP directory service, an X.500 based ITU recommendation, which stores not only common user data but additionally all organisational groups and functional roles. For distinct use cases, an online version (HTML) as well as a print version (PDF) for non-networked working environments and a data integration version (XML) of the SOPs for data integration with external knowledge bases are available.

5 Results

Having a centralized infrastructure proved to be a great advantage over excessive e-mail communication regarding layout consistency, versioning and archiving. At present, the SOP-Creator has been adopted for the creation of 84 SOPs in the application area of malignant lymphoma[8]. For this effort, 10 editors at five sites across Germany are working together, and their feedback directly influences the ongoing development of the SOP-Creator. Other competence networks like heart insufficiency and the coordination center for clinical trials Leipzig consider a deployment. One problem arose: SOPs are non-formal documents. Therefore, they cannot easily be checked for semantic errors like reference cycles and inconsistent usage of terms.

It showed up that quite a bit of time was required for training quality managers to use the web-based content management system, mainly because they were used to use a comfortable text processor like MS Word. It was helpful that most other medical documents for ongoing clinical trials like synopsis, flow sheets, study protocols and ethic approvals are also maintained via the CMS. Hence, it can be concluded that knowledge distribution by means of a web application based on a CMS is not to hard to utilise for an average users.

6 Further Developments

In addition to the routine operation of the SOP-Creator, new capabilities are being implemented in order to expand the SOP-Creator's application range and to improve its usability. That includes the

1. *structural analysis of an SOP's content*. Presently, SOPs are loosely structured documents. They are composed of natural language. Therefore, there is no formal structure but only flat, paragraph-based text with structural tags like headings and logical tags like abbreviations. To improve workflow support and to enable an easy instantiation of working instructions, it is important to declare an SOP (and its paragraphs) in terms of a task-consisting-of-sub-tasks-relation. Furthermore, simple references to corresponding SOPs must be extended to typed links that characterise the underlying kind of this relationship.

2. *the semantic annotation of mark-up elements* for context-oriented presentation using RDF. Different users need different granularities and context-specific views of SOPs. There are target groups that differ in knowledge (medical practitioner, study nurse, documentation staff) or that differ in skills (expert, advanced, novice). Embedding machine-readable meta information allows the transformation of SOPs in respect of different levels of detail. Marking changes made by authors and weighting the quality of the fragments edited could lead to a RDF semantic network of experts parsed from audit trail entries.

[8] http://sops.kompetenznetz-lymphome.de/

3. *the integration of terminology reference systems* via web services (e.g. the Onto-Builder's Data Dictionary [He04] or Wikipedia). In medicine, many terms have no unambiguous meaning. For example, in case of disseminated decay of organs, if both kidneys are affected, it is unclear whether that is counted as one or as two different occurrence of organ decay. To offer references to detailed, semantically founded definitions [HHL04] and to harmonise trial parameters, it is useful to provide an integration with software that can help to establish a consolidated ontology for clinical trials.

4. *the expansion of the "SOP" concept* to a more generic, abstract document concept (information meta model) from which concrete document types like clinical guidelines, SOPs and working instructions can be derived.

Acknowledgement: The Federal Ministry of Education and Research (BMBF) has supported this work (grant no.: 01GI9995).

List of Literature

[AMB01] Abecker, A., Maus, H., Bernardi, A. Software-Unterstützung für das Geschäftsprozessorientierte Wissensmanagement. 1. Konferenz Professionelles Wissensmanagement (WM2001), Baden-Baden, March 2001.

[Amg04] Zwölftes Gesetz zur Änderung des Arzneimittelgesetzes. BGBl I 2004, 2031. Version July 2004.

[Ha00] Harnischmacher U., Wendland G., Ludwig D., Dinghaus P. Standard Operating Procedures für die Klinische Forschung an Universitäten. Informatik, Biometrie und Epidemiologie in Medizin und Biologie 2000; 31(3):92-102

[He04] Heller, B., Herre, H., Lippoldt, K., Löffler, M. Standardized Terminology for Clinical Trial Protocols Based on Ontological Top-Level Categories. In (Kaiser, K., Miksch, S., Tu, S.W. eds.) Computer-based Support for Clinical Guidelines and Protocols. Proc. of the Symp. on Computerized Guidelines and Protocols. (CGP 2004), Prag, 2004. IOS-Press, Amsterdam, 2004; p. 46-60

[HHL04] Heller, B., Herre, H., Lippoldt, K. The Theory of Top-Level Ontological Mappings and its Application to Clinical Trial Protocols. In: Motta, E., Shadbolt, N., Stutt, A., Gibbins, N. (eds.) Engineering Knowledge in the Age of the Semantic Web: Proceedings of the 14th International Conference (EKAW 2004), Whittlebury Hall, UK, Oct 2004. Lecture Notes in Computer Science, Springer, Berlin, Vol. 3257, p. 1-14.

[ICH96] ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice (GCP) E6: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996.

[Pfi03] Pfistner, B., Mehl, C., Klöss, M. Löffler, M., Herrmann-Frank A., Diehl V.. Qualitätsstandards und ihre Sicherung für Studienzentralen im Kompetenznetz Maligne Lymphome. Klinische Pädiatrie 2003; p. 215: 341-344

[PR95] Picot, A., Rohrbach, P. Organisatorische Aspekte von Workflow-Management-Systemen. Information Management. H. 1/1995; p. 28-35.

[Sch01] Schwarz, S., Abecker, A., Maus, H., Sintek, M. Anforderungen an die Workflow-Unterstützung für wissensintensive Geschäftsprozesse. 1. Konferenz Professionelles Wissensmanagement (WM2001), Baden-Baden, March 2001.