QUALITY IMPROVEMENTS FOR READING CENTRES
Methods to Improve Quality and Compliance using Computerised Systems

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Abstract: Reading centres are a concept to enhance the results and the acceptance of clinical trials. Computerised systems provide the possibility to improve reading centres in a significant way. However ophthalmic reading centres often do not fully use the potential of computerised systems. In this paper we show some of the advantages sophisticated software can provide over traditional methods like e-mail. The improvements can be structured in the following categories: Decreasing the chance of human mistakes; optimizing data exchange and data flow; enforcing SOPs and complex workflows; further improvements. Large parts of the proposed methods were successfully implemented in a proof of concept system for the Tuebingen ERG Reading Centre that can serve as a reading centre in large ophthalmologic multi-centre clinical trials.

1 INTRODUCTION

The need for constantly high quality results in clinical trials leveraged the application of reading centres. In a reading centre especially trained experts analyze technical examinations. This offers several advantages for the analysis of clinical trials, like high quality results, invariably interpretation of the measurements and a wide acceptance of the results. Furthermore the concept comes with more general advantages like omitting the need for especially trained reading personnel at the local sites, fast turnaround times, highly tested and broadly accepted standard operating procedures. Although those advantages are already present in single-centre trials, the effects of most of them are significantly higher in multi-centre clinical trials. Reading centres can therefore be seen as a quality improvement instrument for the conduction of clinical trials.

Computerised systems changed the conduction of clinical trials radically, nevertheless at present many existing reading centres in ophthalmology still rely on traditional concepts, e.g. the ubiquitous communication via e-mail as the electronic equivalent to communication by mail. Unfortunately e-mail is much more insecure which is especially a concern if source data and reading results are exchanged in this way. Oftentimes the workflows and processes in the centre are still manually coordinated which not only causes much effort for the organisers but also boosts the risk of human mistakes.

We believe that with modern software technology it is possible to enhance reading centres in a significant way. All presented methods either improve the reading results or contribute to maintain study protocol compliance and hence improve the reading centres' quality considerably. In order to bail out the full potential it is assumed that all source data is submitted in electronic form.

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The methods we propose are structured in categories as follows: Decreasing the chance of human mistakes; optimizing data exchange and data flow; enforcing SOPs and complex workflows; further improvements. We will close with a short conclusion.

2 QUALITY IMPROVEMENTS

2.1 Decreasing the Chance of Human Mistakes

Great potential regarding quality improvement lies in the elimination of "human factors". Of course a reading centre is not possible without human participation but the personnel should be able to concentrate on the core task - that is the reading of technical examinations - and not on support processes.

One example for such a support process is the anonymization of patients during the reading process. To guarantee the objectiveness of the actual rating it is necessary to hide not only the name of the local site which submitted the data but also to provide the examination data initially without any patient context to the reader. After this first reading the data can be provided again with the patient context, hence with past examinations and reading results. The patient ID within the reading centre naturally has to differ from the patient ID the local site uses. Therefore a pseudo ID which is only valid within the reading centre has to be provided for the history check. This de-personalization is very error-prone if done by humans. Furthermore it is questionable at which point in the reading process it should be done. If nobody at the reading centre is allowed to know the real IDs of the patients and the software does not support this process it must occur at the local site. However this may be confusing for those persons who coordinate the exchange between the local site and the reading centre, because they have to remember at least two IDs per patient. This becomes even worse if the local site submits source data to more than one reading centre. This implies the danger of mixing the IDs up during communication with the reading centre. If this part is handled by the reading centre software, it can be absolutely transparent to local sites and the reading centre personnel. The local sites can use their well known IDs when submitting or querying data. The software generates new pseudo IDs for the use in the reading centre in the background without human action. Furthermore the software can show or hide this ID to readers dependent on the process context. Thus the de-personalization by the reading centre software does not only eliminate a source of possible human mistakes but also enhances the comfort for all participants.

Other examples for human mistakes are simple spelling mistakes which are as trivial as common. However they can be automatically identified up to a certain level and the user can be notified immediately and the mistake can be corrected just in time. This does not only improve the data quality but also reduces unneeded iterations of input processes and thus enables faster turnaround times.

2.2 Optimizing Data Exchange and Data Flow

Many reading centres still rely on e-mail communication. This is problematic for several reasons. First and foremost unencrypted e-mail communication is very insecure and not comparable to traditional mail. Before an e-mail reaches its recipient it is usually processed by many servers. Unfortunately an e-mail usually has, if it is not encrypted, no envelope like a letter and everybody on its way from the sender to the recipient can read subject and body of the e-mail. More badly this happens unconsciously. If the e-mail has no digital signature, it would be even possible that the content of that e-mail changed unconsciously. Both problems can be addressed with modern cryptography, but this introduces great complexity and effort for the users and therefore is hardly used in practice.

Another problem of e-mail communication is that it is not observable and therefore not tracked in an audit trail. However the traceability of all actions during the study is a common requirement. E-mail communication and even more data exchange via e-mail are therefore often inapplicable.

Since the e-mail content is innately not structured the reading centres' standard operating procedures (SOPs) have to define some kind of template which is to be applied by the users. But this way automatic parsing at recipient side becomes very difficult because excessive exception handling is needed to catch user-made deviations from the defined format.

Beside these technical reasons e-mail communication is uncomfortable for the users at the local sites as well as at the reading centre. For e-mails usually programs are used, which are not dedicated or customized for clinical trials. Not only can the reading centres' e-mails mix up with unrelated e-mails, but also the possible support for

the users is underachieved compared to a specialised program.

If the reading centre is implemented as a web application with secured and encrypted access via https these disadvantages can be completely eliminated. In this case e-mail is hardly necessary for communication and in no case for data exchange. Instead local sites get a special account for uploading source data and querying reading results; of course all encryption and digital signing takes place in the background without explicit user action and all actions are fully tracked in an audit trail. The software also takes care of transferring the data to the correct recipient within the reading centre which disburdens human coordinators and thus eliminates risks of human mistake. Since the web application is tailored for the requirements of the reading centre, every member is supported in an optimal way in accomplishing their tasks. Additionally the reading centre business is kept separated from unrelated work.

2.3 Enforcing SOPs and Complex Workflows

Every study protocol defines a set of SOPs describing the workflows before, during and after the trial conduction. The reading centre personnel have to follow all these rules strictly and without the slightest deviation. Unfortunately it is hard to track in detail if these rules are always followed as they should. In an electronic reading centre parts of these SOPs can be digitally modelled as workflows. Then the reading centre software can take care of enforcing the processes at all time, thus enhancing the compliance with the SOPs by eliminating deviations.

Also workflows become possible which would be too much effort to implement without electronic support. Especially those complex workflows have great potential to raise and maintain overall results quality.

One example for such a workflow is a parallel independent double reading of each examination by two readers seen in Figure 1. The software can compare both results afterwards and notify a senior reader if they differ significantly. This reading workflow greatly reduces the possibility of subjective reading results. If the work introduced by double reading is too expensive, it is also possible to let the software assign this sophisticated workflow only to random examinations or to directly assign the senior reader check to random examinations without double reading.

As mentioned before it is indispensible to read the examinations first without the context of a patient in order to guarantee the most objective reading result possible. However in this case the reader does not know the history of the patient and has no possibility to compare the examination to past measurements and it is possible that slight deterioration of measured values is overlooked first. To eliminate this disadvantage without losing objectiveness the old examinations and reading results can be shown only after the reading has been completed and closed. This history check can easily be implemented electronically but would be much effort to be ensured manually.

Since the goal of reading centres are constantly high quality results, the result of one particular examination should be invariant. In order to assure a constant quality it is necessary to track whether it makes a difference when they are read. For this purpose an automatic re-reading, either by the same

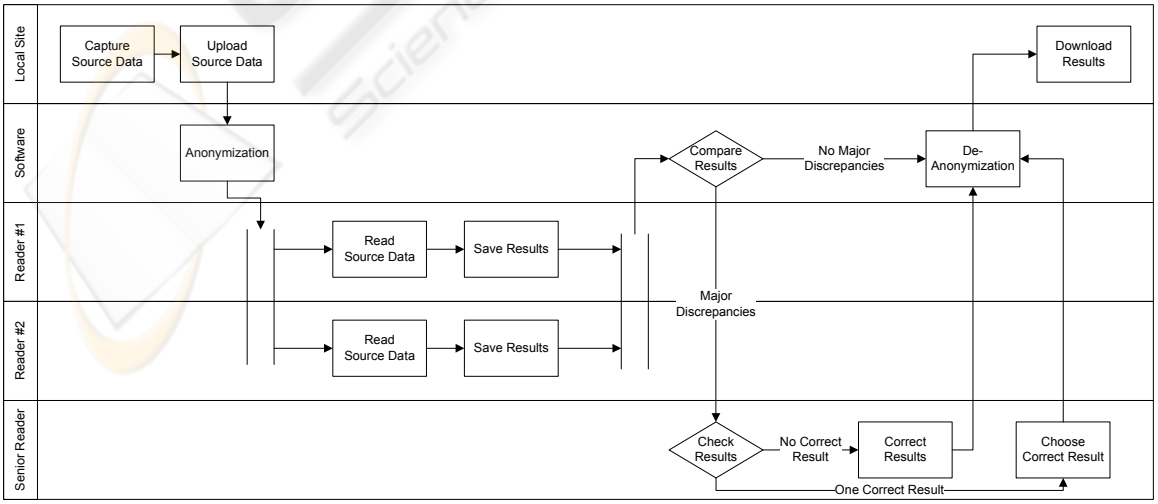

Figure 1: Workflow for parallel independent double reading.

or by a different reader, of old cases after some time is suitable. This enables the tracking of the reading quality over time and is a great quality assurance method which would be hard to do without electronic support.

2.4 Further Improvements

Great potential of electronic software support lies in the possibility to automate routine tasks like notifications and thus disburden human coordinators.

The software can automatically notify a reader when a local site submitted an examination for reading or the local site when an examination has been read. Every actor in the reading process is notified at the right point of time, so there is no need for manually checking to-do lists. This enables higher turnaround times because of minimal waiting time.

For high quality reading results the data quality of the source data is crucial. Therefore it is mandatory to approve all local sites prior to their first submission of real data. Usually this is done by submitting several sample examinations which then are tested for eligibility. Great parts of this certification can be automated, e.g. the check for completeness of the submissions.

Not only is the source data quality important but also the data quality at every point of the reading process. Wherever possible the software should observe it. As already mentioned spelling mistakes are quite common and to some level the software can automatically notify the user about them. There are more mistakes of that kind. For example it can happen that the source data does not suffice the needed quality standards, e.g. because of missing measurements or being in an invalid format. If the source data format is well defined the reading centre software can automatically reject the submission and notify the local site. Reading results can be wrong due to various reasons, too. Again the software can inform the reader in the case of implausible results.

Beside that the reading centre software can observe the examination and reading values over time and notify the senior reader if they drop out of predefined ranges or worsen by a predefined percentage rate. This helps to ensure that all adverse events are noticed.

Furthermore it is possible to enforce an ongoing training of all reading centre members. The software system can be used for this purpose, e.g. by discussing sample cases in a group. Not only can the requirement of continuous training be fulfilled this way. Also a common way to rate examinations is created, which asserts a constant quality regardless of the particular reader. This becomes even more relevant if difficult real-world cases are used for this training. The acceptance of the training among the personnel may be enhanced by integrating the training cases via e-learning into the normal day-to-day work of the reading centre.

3 CONCLUSIONS

Reading centres are a good way to enhance the quality and acceptance of clinical trials. Although computerised systems have the potential to drastically improve the delivered quality, in ophthalmic reading centres specialised software is rarely used. Instead many centres still rely on e-mail communication and manual coordination of the reading process. In this paper we proposed several possibilities how a specialised software system can improve the quality and compliance of a reading centre.

Large parts of the proposed methods were successfully implemented in a proof of concept system for the Tuebingen ERG Reading Centre at the Institute for Ophthalmic Research, University of Tuebingen. For the actual implementation Nuxeo, an Enterprise Content Management (ECM) System which provides a reliable basis for data storage, workflow management and permission management, was used. This ECMS was heavily customized to fulfil the requirements of modern reading centres. The result is a sophisticated software system, which not only ensures high quality results and study protocol compliance, but also greatly improves the comfort for both the local sites and the reading centre members.

Further advantages will emerge if the software manages not only one single reading centre but the whole study like proposed in (Strasser *et al.*, 2008). This way all information is kept in a single repository, superseding the need for data exchange between different systems used during the trial.

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