Knowledge acquisition for clinical trial phase categorization

Anja S. Fischer, Gertraud E. Markl, Ulrich Mansmann

Institute for Medical Informatics, Biometry and Epidemiology, University of Munich, Munich, Germany

Abstract and Objective

Phase classification is crucial for correct assessment of the scope of a clinical trial. The Ripple Down Rules method is used to develop an automated decision support system for classification. After training by human experts, the automated classification responses of the system are evaluated.

Keywords:

Clinical phase, Trial, Knowledge acquisition, Ripple Down Rules

Introduction

Clinical trials are classified by a sequence of phases during the drug development process. This classifier allows a fast assessment of the basic purpose of a trial. The temporal interpretation of phases is considered to be insufficient and therefore it was suggested to classify trials by the study objectives [1]. The classification comprises of 4 main phases (Phase I-IV). The phase of a trial has to be officially declared when requesting approval by authorities and review boards.

Victor stresses that a correct integration into the drug development process is essential for the ethical tenability of the trial [2]. However, the phase classification of research-driven or investigator-initiated trials often bears the need for discussion and clinical research experts are required for interpreting different relevant guidelines [1, 3]. As of yet, an interactive tool supporting the phase classification doesn't exist. In this project such a system was developed.

Methods

Phase classification depends on trial design parameters. For acquiring knowledge about which parameters are crucial we use the Ripple Down Rules method. It was proposed in 1988 by Compton and Jansen and it results in a rule based expert system. It has been successfully used to build a large medical expert system [4]. The knowledge of interviewed experts is added to the existing rule base in a context-dependent manner.

We decided to use this approach for two reasons: 1) The trial design parameters and their values crucial for classification don't have to be defined in advance. A new criterion can be added at any time during training and production phase.

2) Trial protocols and design parameters often have to be kept confidential. The expert has to be able to add his knowledge in the form of classification rules to the system without discussing it with a knowledge engineer.

A web application to implement the Ripple Down Rules approach for acquiring knowledge from clinical research experts was developed based on standard components.

Results

For knowledge acquisition two experts processed 46 interventional trials of two medical domains (uniformly distributed across phases). The training process resulted in 16 classification rules. A system evaluation was conducted using 12 interventional trials from various medical domains. Classification of a human expert was used as gold standard. 5 trials were classified correctly and 7 classifications failed.

Conclusion

The evaluation showed results inferior to what was expected. Classification rules differ according to medical domains so that the external and internal validity of training and test cases has to be examined. The involved experts often differed in the scope of interpretation of clinical research terms i.e. "pharmacodynamics". The system often failed in trials which are difficult to classify also for human experts and correct classification in absolute terms is subject to discussion.

References

[1] International Conference on Harmonisation (ICH). E8 - General considerations for clinical trials; 1997

[2] Victor N. Prüfung der wissenschaftlichen Qualität und biometriespezifischer Anforderungen durch die Ethikkommission? MedR Medizinrecht. 1999;17(9):408-12.

[3] Turner JR. New drug development: design, methodology, and analysis: Wiley-Interscience; 2007.

[4] Preston P, Edwards G, Compton P. A 2000 rule expert system without a knowledge engineer. In: AIII-Sponsored Banff Knowledge Acquisition for Knowledge Based Systems; 1994; Banff; 1994.