Author's response to reviews

Title: The AQUA-FONTIS Study: Protocol of a multidisciplinary, cross-sectional and prospective longitudinal study for developing standardized diagnostics and classification of non-thyroidal illness syndrome.

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Second revision according to your request from September 30th, 2008.

Non-thyroidal illness syndrome (NTIS) is a common condition in critically ill patients. However, diagnosis and classification of NTIS are still dissatisfactory, and in consequence therapeutic trials often lead to contradictory results. The AQUA-FONTIS study is a trial that aims in ameliorating this situation by development of an unambiguous diagnostic definition and classification of NTIS.

This study is faced with certain challenges that are characteristic for emergency and intensive care research, first of all the inability of most patients to give informed consent timely. We solved this problem by a study-structure that consists of two modules, one that is purely observational and a second, more far reaching, that is performed after patients consented in participation. Therefore the study can be conducted while the moral principle of nonmaleficence is fulfilled. Neither the ethical principles of autonomy, beneficence and justice nor legal requirements of German law governing clinical trials of drugs and medicinal products (Arzneimittelgesetz) nor the corresponding European directives 2001/20/EC and 2005/28/EC are applicable to this kind of study. Therefore the AQUA FONTIS study may be a model for future trials in the field of observational and diagnostic research in critical care.

This manuscript and its parts have not been published in or submitted to another journal or conference proceedings. All authors have read and agreed to its content, the study protocol has been approved by the local ethics committee of the Ruhr-University of Bochum. The authors have no conflicts of interest.

We decided in favour of early submission of this study protocol in order to support initiatives against publication bias.