

Predicting Methodological Quality of Non-Profit Clinical Trial Protocols: A Multicentre Extension

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INTRODUCTION

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement has long been the international reference for the content of clinical trial protocols, ensuring transparency, methodological rigour and ethical soundness [1]. The recent release of SPIRIT 2025 has updated and expanded its recommendations [2]. Nonetheless, numerous studies continue to document suboptimal adherence, particularly regarding study design and statistical analysis. Assessing real-world adherence helps identify recurrent shortcomings and areas requiring targeted support or training.

OBJECTIVES

In a previous single-centre study we assessed whether it is possible to predict which protocols show high adherence to the methodological SPIRIT items, identifying study-level characteristics associated with quality. The main limitation was the single-centre nature of the data. The present work extends the analysis to a multicentre design, combining protocols from two Italian research centres: Fondazione IRCCS Policlinico San Matteo (Pavia) and IRCCS Sacro Cuore Don Calabria (Negrar di Valpolicella, Verona), aiming to confirm the predictors of adherence and improve their generalisability.

METHODS

Design and methodological features of no-profit interventional protocols submitted between 2021 and 2025 to the reference Ethics Committees of the two centres were collected and recorded in a centralised REDCap (Research Electronic Data Capture) database. Adherence was assessed on the SPIRIT 2013 items concerning methods, design, data collection and management, and analysis (items 9-21b); the 2013 version was used because all protocols predate SPIRIT 2025. Each item was scored as fulfilled or not, and an individual score was computed as the number of satisfied items, dichotomised at the median into good and poor adherence. For the predictive objective, machine learning algorithms (Random Forest, eXtreme Gradient Boosting, Boosted Logistic Regression) were applied to a pool of candidate predictors; performance was evaluated through accuracy, area under the ROC curve (AUC) and F1 score. Variable importance was then summarised and the most influential predictors were entered into a multivariable logistic regression model, reporting odds ratios and 95% confidence intervals. Covariates included sponsorship, methodological features, submission timing and thematic area. Analyses were performed using Stata 19 and R 4.4.3.

RESULTS

Data collection and harmonisation across the two centres are currently ongoing. The IRCCS Sacro Cuore Don Calabria

contributed 107 no-profit interventional protocols submitted to its reference Ethics Committee between 2021 and 2025. Combined with the 132 protocols of the previous single-centre study, the pooled cohort reaches 239 protocols. This larger and more heterogeneous sample is expected to produce more stable predictive models and to enable a formal assessment of the reproducibility of the predictors identified in the single-centre analysis. We expect to confirm the availability of statistical and methodological support as a factor associated with good adherence, while the relative contribution of the remaining candidate predictors (sponsorship, methodological features, submission timing and thematic area) will be clarified in the pooled cohort. The machine learning algorithms are expected to discriminate good from poor adherence and to converge on a consistent subset of influential predictors, which the multivariable logistic regression should retain as independent. The final estimates will be presented.

CONCLUSIONS

The multicentre extension addresses the main limitation of the previous work, strengthening the external validity of the findings. By integrating conventional statistical approaches with machine learning models, the study aims to clarify which protocol features predict high adherence to SPIRIT and to confirm the role of multidisciplinary teams, including biostatisticians, in improving methodological quality. The findings are expected to provide evidence to inform training strategies aimed at improving the quality of clinical trial protocols.