

# Statistical Monitoring of Clinical Trials with Time-to-event Endpoint: Conditional Power, Interim Forecasting and Application on a Case Study

Ratti Edoardo<sup>1,2</sup>

Galimberti Stefania<sup>1,3</sup>

Valsecchi Maria Grazia<sup>1,3</sup>

1 *Dipartimento di Medicina e Chirurgia, Università Milano-Bicocca.*

2 *Center for Research on Health and Social Care Management (CERGAS), Università Bocconi.*

3 *Centro Interdipartimentale BICOCCA BIOINFORMATICS BIostatISTICS AND BIOIMAGING CENTRE - B4*

## Introduction

An important aspect in the design of a randomized clinical trial is the planning of analyses of outcome performed on accumulating data while the study is in progress, i.e., interim analyses, a common approach to ensure trial adaptivity for ethical and scientific motivations [1]. There are standard and novel statistical methods employed in interim analyses. Standard methods refer to the group sequential approach, whose objective is to monitor the study in terms of early efficacy or early futility by controlling the inflation of the probability of type I error and stopping the trial if early efficacy or early futility is detected. Widely used approaches in this area are the alpha-spending function and the Conditional Power (CP). However, in calculating both, the information fraction at each interim and at the final analysis should be correctly approximated. From this perspective, planning and executing the interim scheme in clinical trials with time-to-event endpoints (CTTE) is challenging since the information fraction and target sample size are function of the numbers of events and not simply of the number of patients enrolled. Therefore, it is crucial that the study provides sufficient follow-up to observe the number of events necessary to preserve the power and the information levels established at the design stage, especially in a maximum duration trial [2]. Given these challenges, standard methods alone are not sufficient to properly monitor a CTTE. Novel approaches were developed to respond to these needs. They refer, among others, to the forecast of the number of events that will occur at a future date, called in the literature as time to endpoint maturation (TTEM), by also considering the ongoing recruitment [3] [4]. However, in the biostatistical literature there is little attention in forecasting the cumulative number of events (CNE) expected at a fixed future date, a well-established area of methods in the reliability analysis literature and referred as within-sample forecasting (WSF) [5].

## Objective

The objective of this work is to develop and validate a statistical model for WSF and for predicting the TTEM in a context of an ongoing CTTE, by providing also forecasting intervals for both the CNE expected at a fixed future date and the TTEM. The model also takes into consideration the possibility that accrual is still opening at the time of the forecasting. A secondary aim is to compare the developed model with CP in terms of their ability to provide the Trial Data Analysis Committee (TDAC) with the most complete information on the study progress and success.

## Methods

We develop a forecast model in the frequentist framework starting from a modeling approach from the reliability analysis literature and a recent and innovative work [6] [7]. The proposed model allows to derive in a closed form the point-wise forecasting interval for the CNE and for the TTEM, assuming an exponential distribution for time-to-events and a homogeneous Poisson process for accrual modeling. Validation of the model was performed by sub-setting the data into four artificial interim time: the CNE at successive interims was predicted by adding the prediction intervals and compared with the number observed. Next, the CP under three different future trends was calculated, i.e., assuming that the null hypothesis, the alternative hypothesis or the current trend observed so far will prevail in the remaining fraction of information. Finally, the ability of the proposed model and the CP to address the issues related to the trial progress is discussed.

## Results

A phase III randomized trial was analyzed at the second interim (information fraction 33%) to forecast the CNE at the final analysis and the TTEM, after verifying that the exponential assumptions were satisfied. Results indicated that the target number of events will be reached after two years of potential follow-up, based on the lower limit of the 95% forecast interval for the CNE. Retrospective analysis at the artificial interim analysis shows that the developed forecasting intervals includes all the values observed, but the performance of the point prediction is not satisfactory as that of the intervals (Figure 1). Calculation CP under the alternative hypothesis and the current trend shows promising results, 92% and 97% respectively. However, the CP under the null hypothesis is equal to 17%, suggesting that the change of failing to declare the superiority of treatment at the final analysis is not entirely ruled out.

## Conclusions

In this work, we have shown the importance of integrating two different approaches for monitoring time-to-event clinical trial, i.e., the CP and a model for WSF based on accumulating data, since they provide complementary answers. For a maximum duration trial, the CP assume that the final analysis coincides with the time at which the target number of events will be observed. Therefore, is important to predict both CNE at future time and TTEM with the proper forecasting intervals. The developed model has strength and weakness. The strength of this work is to have developed a closed form model for forecast both WSF and TTEM in a frequentist framework, by simultaneously considering the ongoing recruitment. Limitations relate to the assumptions of lack of dropouts, constant event rate and a homogenous Poisson process for enrollment. These assumptions were inspired by the case example but may not be applicable to other case studies. These limitations can be overcome with future work.

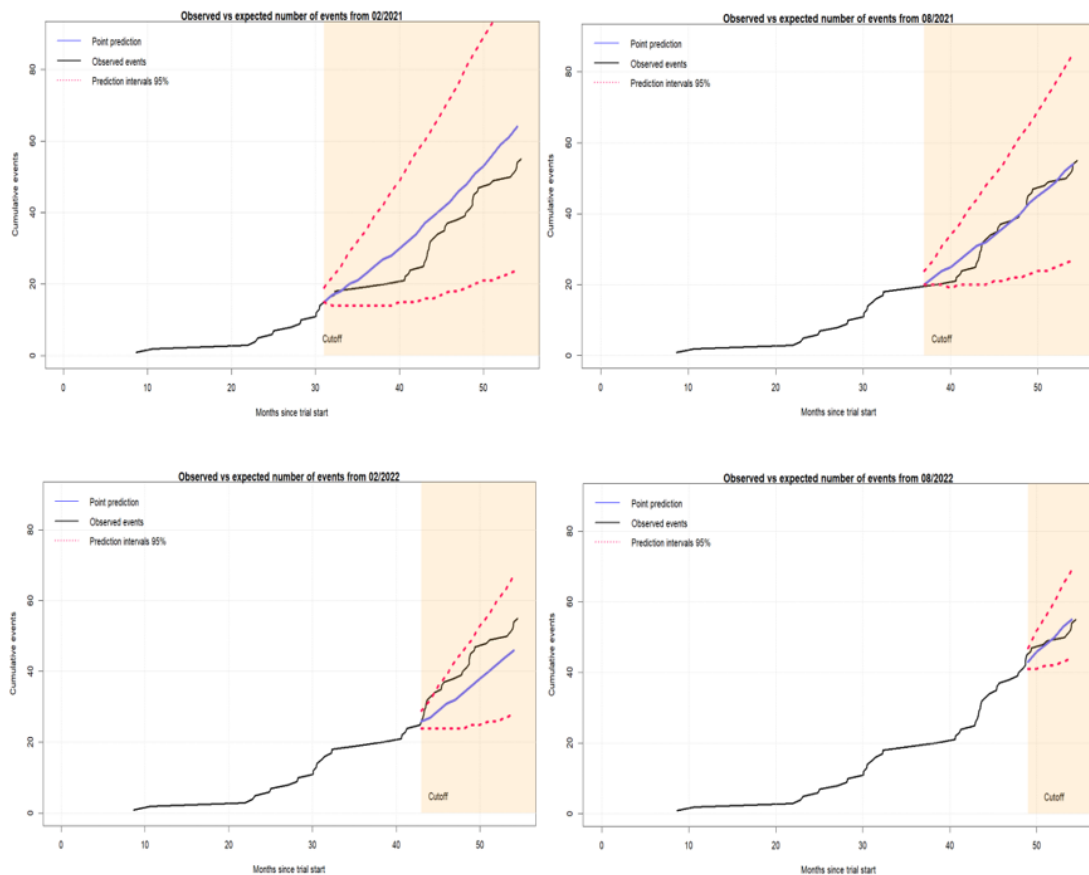


Figure 1: forecasting interval computed at four artificial interim analysis. The yellow shade represents the time in the future from a given cutoff. The black line is the number of events observed at each month since trial start. For each cutoff, the forecasting intervals and the point prediction is computed for future times and compared to the number of events observed in that times.

## References

- [1] Chow S.C., Chang M. (2012). *Adaptive Design Methods in Clinical Trials, Second Edition*, Chapman & Hall/CRC, New York.
- [2] Lan K.K., Lachin J.M., Implementation of group sequential logrank tests in a maximum duration trial. *Biometrics*, 1990 Sep; 46(3):759-70.
- [3] Heitjan D.F., Zhiyun G., Ying G., Real-time prediction of clinical trial enrollment and event counts: a review. *Contemp Clin Trials*, 2015 Nov; 45(Pt A):26-33.
- [4] Wang L., Liu Y., Chen X., Pulkstenis E., Real time monitoring and prediction of time to endpoint maturation in clinical trials. *Statist Med*, 2022 Aug; 41(18):3596-3611.
- [5] Tian Q., Meng F., Nordman D. J., Meeker W. Q., Predicting the Number of Future Events. *Journal of the American Statistical Association*, 2021 Jan; 117(539):1296–1310.

[6] Hong Y., Meeker Q.M., McCalley D.J., Prediction of Remaining Life of Power Transformers Based on Left Truncated and Right Censored Lifetime Data. *Ann Appl Stat*, 2009 June; 3(2): 857-879.

[7] Anisimov, V.V., Gormley, S., Baverstock, R., Kineza C. Advanced models for predicting event occurrence in event-driven clinical trials accounting for patient dropout, cure, and ongoing recruitment. *arXiv preprint*, 2021 Aug; arXiv:2108.09196.