Mediana: R package for power evaluation in clinical trials with multiplicity adjustment methods

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Context

Context

General problematic

- Clinical trials (CT) should be designed to ensure a high probability to detect an effect if the treatment is effective

Sample size calculations in traditional setting

- Traditional CT with two arms, a single endpoint and no interim looks
- Sample size calculations can be done using closed-form expression
- Example for normally distributed endpoints :

$$n_{pergroup} = \frac{2(z_\alpha + z_\beta)^2 \delta^2}{\sigma^2}$$

Context

Sample size calculations in complex setting

- CT sponsors are often interested in pursuing multiple objectives in Phase II or Phase III clinical trials such as :
  - Multiple doses-control comparisons
  - Multiple endpoints
  - Multiple patients population
  - Multiple interim looks
- Multiple testing procedures should be used to control the overall Type I error rate
- General analytical expressions of the power function do not exist in this case

Context

Problematic

- How to evaluate power in clinical trials with complex clinical objectives ?

FDA Enrichment strategies for CT

- *Determining the required sample size that will provide reasonable power to test the different hypotheses while controlling type-I error [...] is challenging*

Simulation-based methods

Key features

- Facilitate decision-making process by answering a wide range of key complex questions
- Quantitative assessment of the performance under multiple scenarios
- Facilitate comparison between competing strategies
- Allow sensitivity assessment and what-if scenario analysis

Clinical Scenario Evaluation framework

Overview

- Developed in Benda *et al.* (2010)
- Decompose the problem of clinical trial simulations into three models

Objectives

- Systematic simulation-based assessment of study designs and analysis methods
- Selection of a robust approach to clinical trial design and analysis which demonstrates optimal performance
- Sensitivity assessment of key parameters

Clinical Scenario Evaluation framework

Key components

- Data model defines the process of generating patient trial data
- Analysis model defines the analysis strategy applied to trial data
- Evaluation model defines the metrics used for evaluating the performance of the analysis strategy

Mediana R package

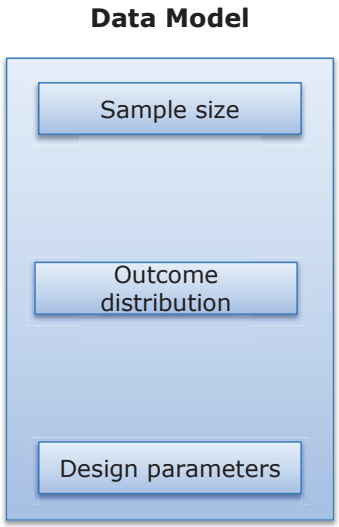
Objective

- Provide a standard framework for power evaluation in clinical trial with high-dimensional statistical problems

Overview

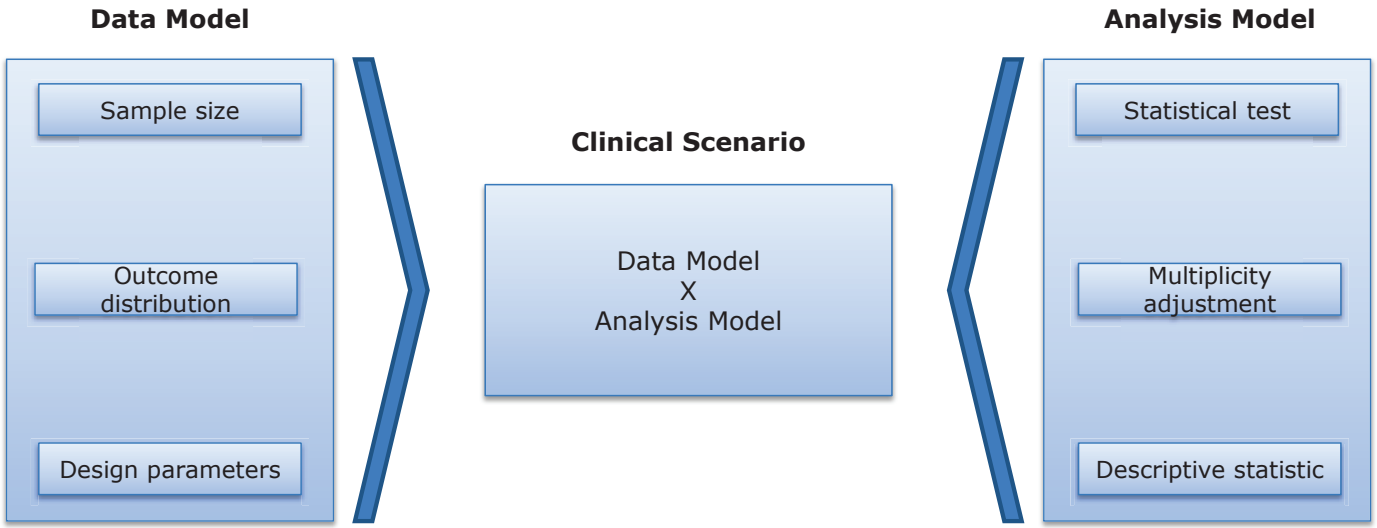
- Based on the Clinical Scenario Evaluation approach
- Support a broad class of data, analysis and evaluation models
- Flexible framework easily extensible to define custom options in data, analysis and evaluation models

Mediana framework

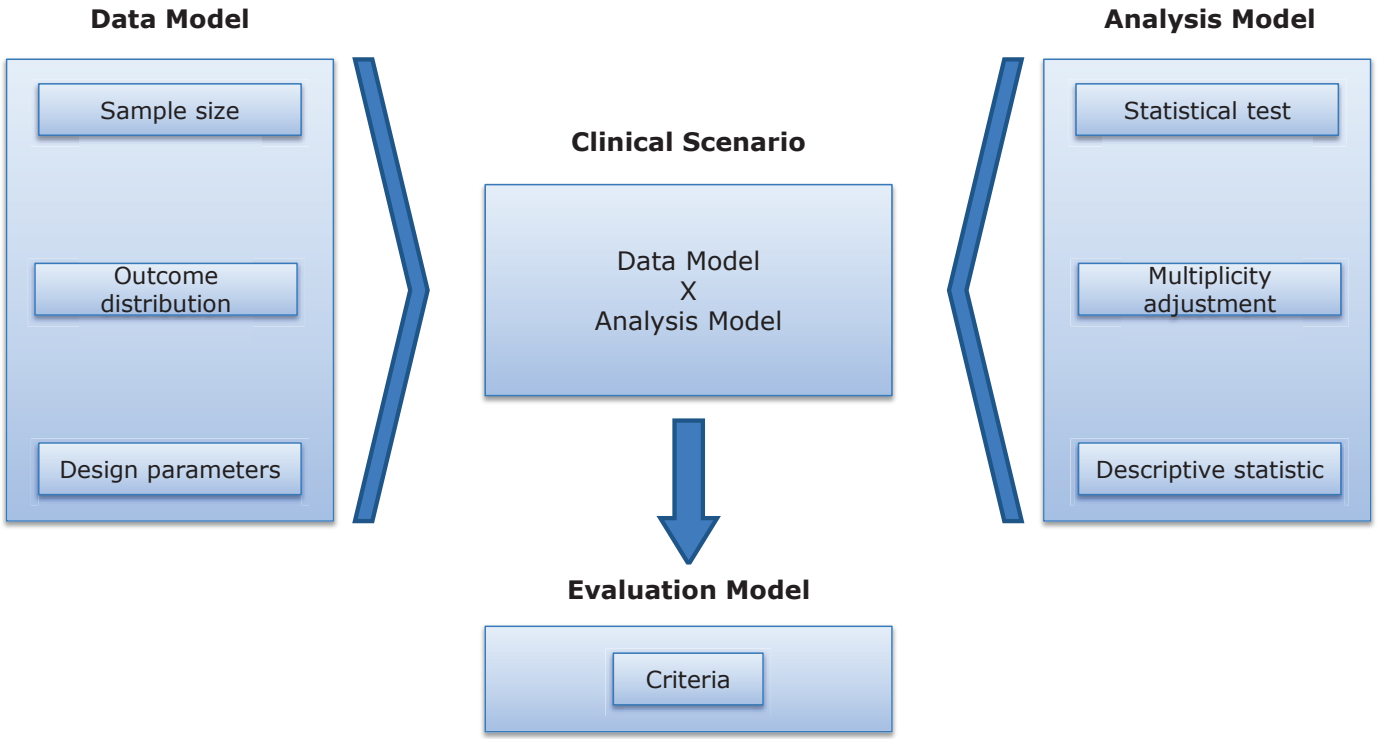


Mediana framework

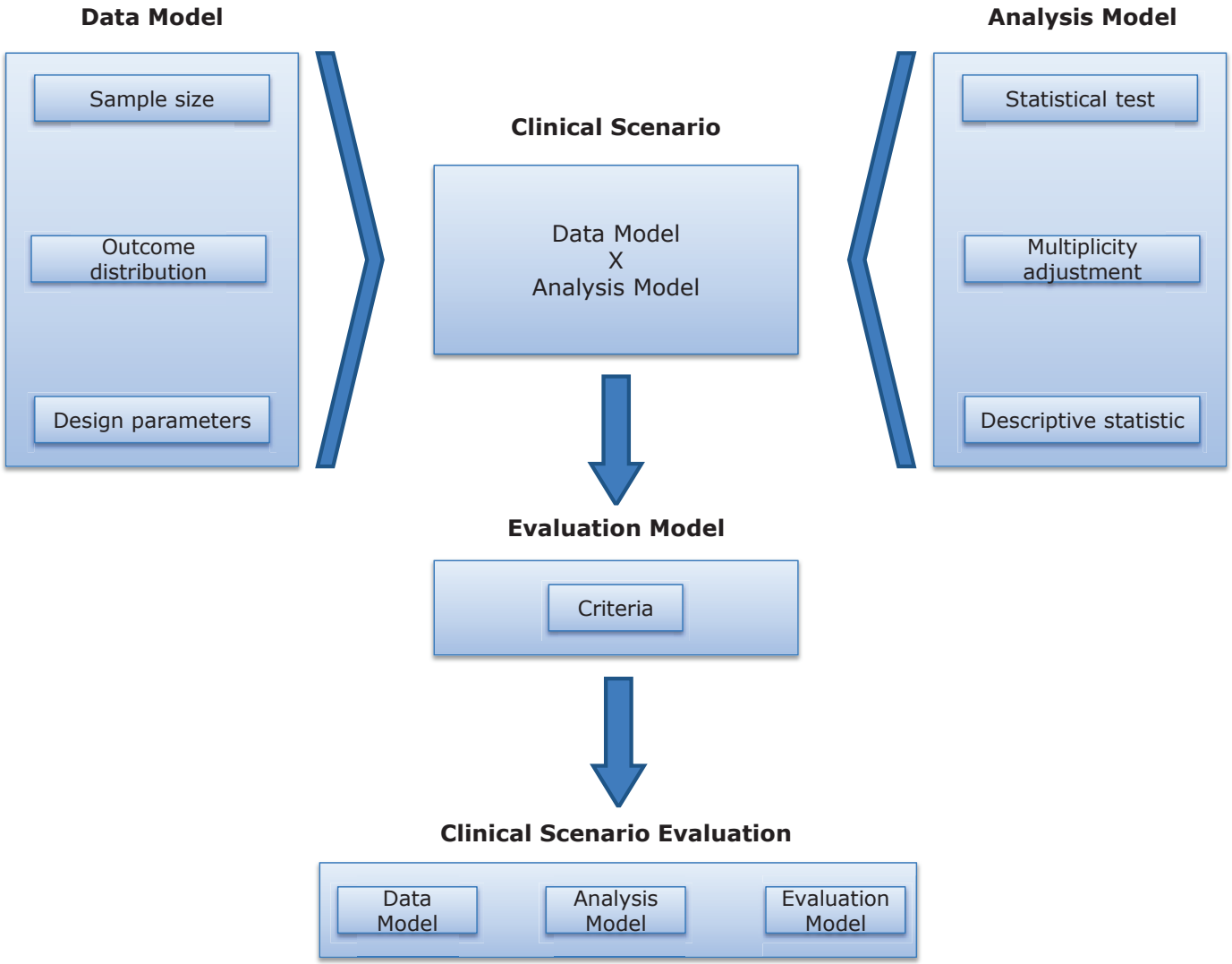
Mediana framework



Mediana framework



Mediana framework



Data model

Endpoint types

- Single trial endpoint (univariate distributions for continuous, binary, time-to-event and count endpoints)
- Multiple trial endpoints (multivariate distributions)

Measurement types

- Single timepoint
- Longitudinal/repeated measurements

Trial design options

- Patient enrollment and dropout modeling

Analysis model

Statistical tests

- Commonly used statistical tests, including parametric tests, nonparametric tests and model-based analysis methods

Descriptive statistics

- Commonly used descriptive statistics

Multiplicity adjustments

- Traditional procedures (e.g. Holm, Hochberg)
- Advanced procedures (e.g. gatekeeping procedures)

Evaluation model

Evaluation criteria

- Broadly used definitions of “probability of successful outcome”

Examples

- Marginal power, disjunctive and conjunctive power
- Metrics based on statistical and clinical significance

User-specified option

Flexible framework

- Mediana package is easily extended to define custom options in data, analysis and evaluation models

Examples

- New endpoint distributions
- New statistical tests
- New evaluation criteria

High-performance computing

Sequential computations

- Simulations are run sequentially on one processor (core)

Parallel computations

- Implemented in Mediana package
- Simulation runs are distributed among multiple processors (cores)
- Substantially reduce computation times
- Easily defined by the user

Reporting

Reproducibility

- Reproducibility is a key point for sponsors and regulators
- Same code will produce the same results

Reporting

- Option to create Word-based summary of simulation results
- Possibility to customize the structure of the summary tables
- Summary data frames allowing graphical representation

When Mediana should be used ?

Clinical trials with...

- ...multiple dose-placebo comparisons
- ...multiple clinical endpoints
- ...multiple patients populations (e.g. overall population and marker-positive subpopulation)
- ...interim analysis (currently not supported)

Case studies

- Visit package's web site for detailed case studies
  `http://biopharmnet.com/wiki/Mediana_package`

Perspectives

Release

- First version is expected to be released in early 2015
- Dmitrienko, A., Paux, G., Brechenmacher, T. (2014). Power calculations in clinical trials with complex clinical objectives. *In press*

New features for next version

- Support to Bayesian methods and adaptive designs
- Interim analysis decision rules for futility or overwhelming efficacy

Key messages

Take home messages

- New drug development is a time-consuming and expensive process
- Need for more efficient drug development programs with innovative designs and advanced analysis strategies
- Crucial role of quantitative assessments of the performance of these designs and analysis strategies
- Mediana R package provides a turnkey solution to facilitate systematic quantitative assessment of performance for Phase II and III trial designs and analysis methods.

References

- Benda, N., Branson, M., Maurer, W., Friede, T. (2010). Aspects of modernizing drug development using clinical scenario planning and evaluation. *Drug Information Journal*. 44, 299–315.
- Dmitrienko, A., Paux, G., Brechenmacher, T. (2014). Power calculations in clinical trials with complex clinical objectives. *In press*.