Clinical trial simulation based on the Clinical Scenario Evaluation framework

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Outline

Clinical Scenario Evaluation (CSE)

Disciplined approach to clinical trial simulation

Software tools

Free software tools that support CSE-based simulations

Case study

Optimal selection of multiplicity adjustments in a Phase III trial

Clinical Scenario Evaluation

Clinical scenario evaluation

General framework

Clinical scenario evaluation (CSE) approach was developed in Benda et al. (2010), Friede et al. (2010) and other publications

Motivation

Clinical trial researchers have recognized the importance of employing systematic and quantitative approaches to evaluating trial designs and analysis methods in clinical trials to enable better decision making

Clinical scenario evaluation

Traditional approach

Trial sponsors often fail to explore plausible sets of statistical assumptions

Gan et al. (2012) reviewed 235 recently published Phase III oncology trials

62% of trials failed to establish a statistically significant treatment effect

Observed treatment effect was almost always smaller than hypothesized treatment effect

Clinical scenario evaluation

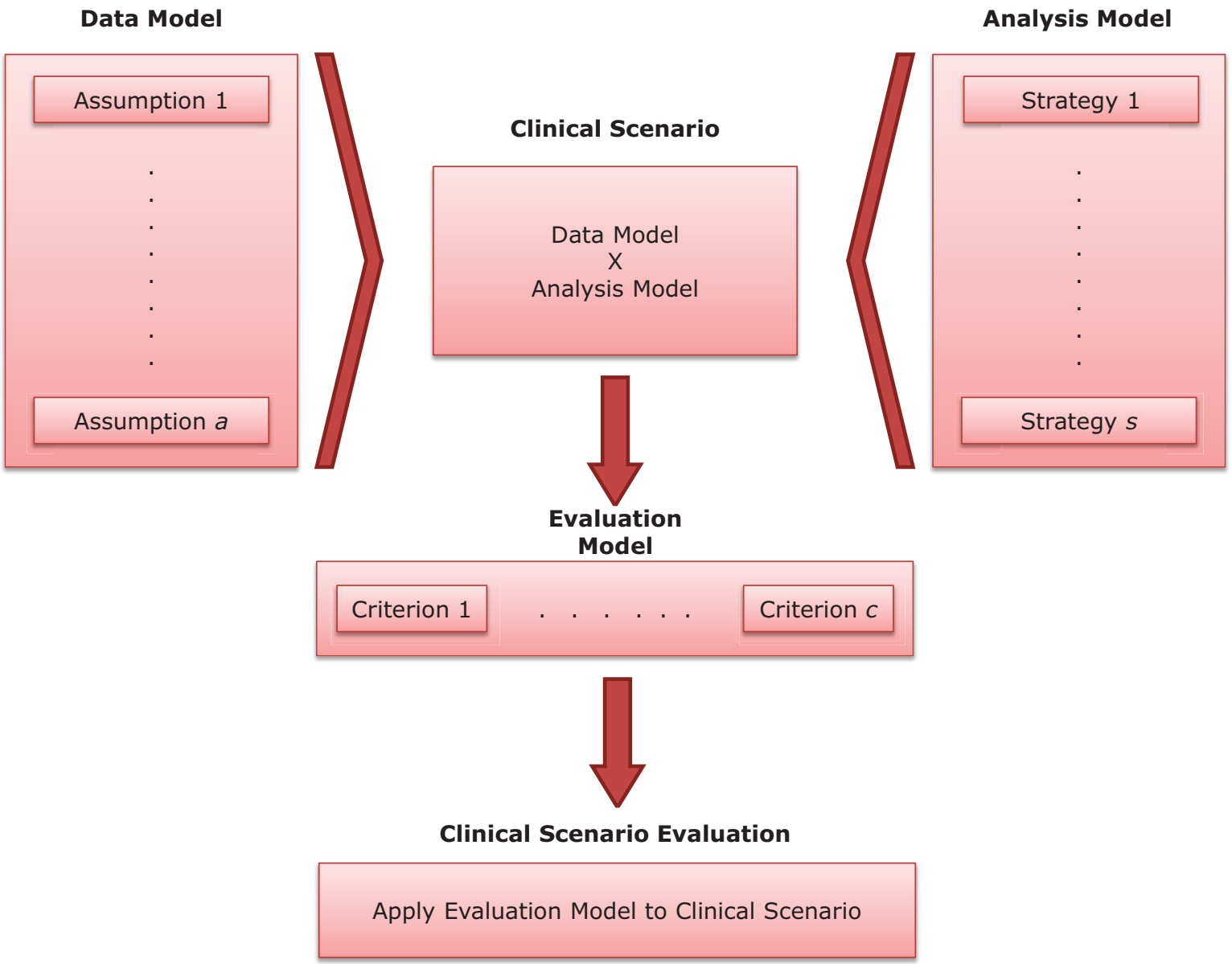
Proposed approach

Critically evaluate the statistical assumptions and analysis strategies to improve the probability of success

Break down a complex problem of clinical trial evaluation to key components (data model, analysis model and evaluation model)

Examine individual and synergistic effects of multiple design and analysis parameters

CSE framework



Software Tools

Mediana (R package)

Goals

Implement the Clinical Scenario Evaluation approach

Provide general framework for clinical trial simulation in late-phase trials (Phase II and III trials)

Support clinical trial optimization aimed at identifying optimal trial designs and analysis strategies

Mediana package

Release

First version was released in July 2015

Current version: Version 1.0.7 was released in July 2018

More information

CRAN web site: https://cran.r-project.org/web/packages/Mediana

Online manual: http://gpaux.github.io/Mediana/

Mediana package

Biopharmaceutical industry

Mediana package is being widely used across the biopharmaceutical industry

Mediana workshops

Mediana workshops/training sessions have been held at several major pharmaceutical companies

Mediana Designer

Description

Free Windows application with a graphical user interface that supports simulation-based sample size calculations in fixed-sample and group-sequential trials using an efficient simulation engine

Biopharmaceutical Software Working Group

Working group sponsored by the ASA Biopharm Section oversees the development of Mediana Designer

Web site: http://biopharmnet.com/biopharmsoft/

Mediana Designer

Release

Pre-release version was released in February 2018

Over 300 statisticians downloaded the software to participate in the public beta test

More information

Web site:
http://biopharmnet.com/mediana-designer/

Efficient clinical trial simulations

Simulation engines

Mediana is an R-based package

Mediana Designer relies on a lightning fast simulation engine written in C++

Example

Size calculations in a time-to-event clinical trial with 10,000 simulation runs

Mediana: Average time is 88.2 sec

Mediana Designer: Average time is 1.2 sec

Clinical Trial Optimization

Clinical trial optimization

Clinical scenario evaluation

An important application of general CSE approach is clinical trial optimization (CTO)

General theme

Utilize CSE to transition from traditionally used approaches to optimal approaches to selecting trial designs and analysis strategies

Inform decision making at different stages of a drug development program to maximize the overall probability of success

Clinical trial optimization

Papers

Optimal selection of multiplicity adjustments in Phase III trials (Dmitrienko, Paux and Brechenmacher, 2016)

Optimal selection of multiplicity adjustments and adaptive trial designs in Phase II and III trials (Dmitrienko, Paux, Pulkstenis and Zhang, 2016)

Book

Clinical Trial Optimization Using R (edited by Dmitrienko and Pulkstenis, 2017)

Case Study

Clinical trial

General information

Phase III clinical trial for prevention of venous thromboembolism (VTE) (Cohen et al., 2016)

Trial design

Novel treatment versus control

Primary endpoint

Composite binary endpoint based on deep-vein thrombosis, nonfatal pulmonary embolism or VTE-related death at Day 35

Clinical trial

Multi-population design

Multi-population design will be used to maximize clinical benefit and optimize patient selection for treatment

Predictive biomarkers

Predictive biomarkers were identified to predict enhanced treatment effect in two subsets of the overall patient population

Clinical trial

Summary of clinical trial results

Population	P-value
Subpopulation 1	0.054
Subpopulation 2	0.029
Overall population	0.006

Fixed-sequence testing procedure: Subpopulation 1, Subpopulation 2 and Overall population

Clinical trial optimization

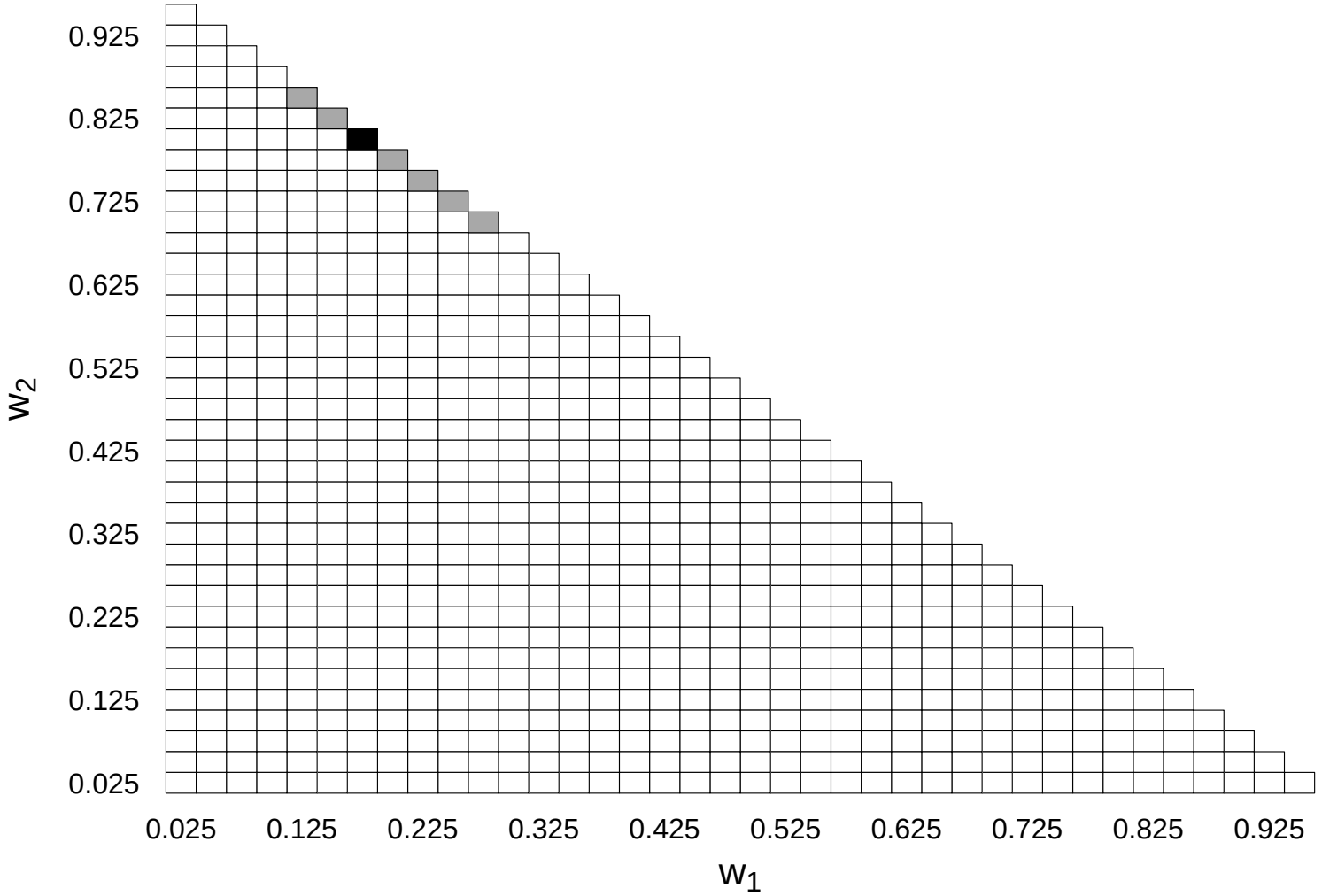
Goal

Select the most powerful and robust multiplicity adjustment in this trial (Paux and Dmitrienko, 2018)

CSE-based approach

Identify plausible data models (weak and strong predictive biomarkers), applicable analysis models (Hochberg procedure with unequally weighted populations) and relevant evaluation model (criteria based on multiplicity penalties)

Optimal selection of population weights



Configuration of weights that maximizes the probability of success

Clinical trial optimization

Sensitivity assessments

Quantitative sensitivity assessments and qualitative sensitivity assessments were performed to identify an optimal multiplicity adjustment that is not overly sensitive to treatment effect assumptions in the three patient populations

Simulation-based evaluation

Simulation-based evaluation was performed using the Mediana package

Summary

Summary

Clinical Scenario Evaluation

General approach to disciplined simulation-based assessments of trial designs and analysis methods in clinical trials

Software tools

Mediana (R package) and Mediana Designer (Windows application) are free software tools that support efficient CSE-based clinical trial simulation

Thank you!

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