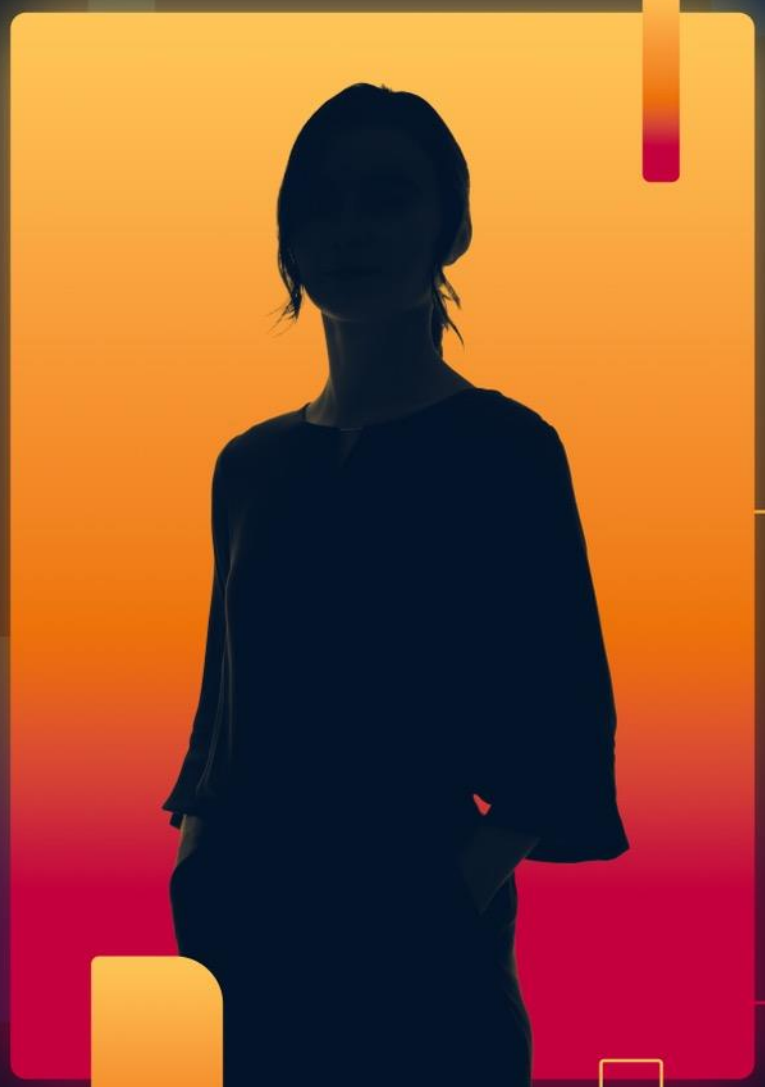

IDDI
DATA WITH PURPOSE

CASE STUDY

Adapting The Randomization Algorithm

Study Description

A randomized phase III trial to evaluate the efficacy and safety of a new drug to treat critical limb ischemia

Indication

Critical Limb Ischemia (CLI)

Patient population

165 adults subjects

Study duration

April 2017 – July 2024

Regions

North America and Europe

Number of sites:

33

Situation

A randomized phase 3 study using a 2:1 minimization algorithm (with 0.8 as the probability) balancing the patients according to minimization factors between 2 arms (Active and Placebo).

Challenges

- The treatment is only manufactured if the patient is randomized to active arm. Treatment is using the bone marrow of the patient.
- If the product cannot be manufactured or is damaged during the transportation, the randomized patient will not be treated.
  - This caused serious imbalance between the two randomized arms for the treated patients.

The Issue

Imbalance between the 2 randomized arms for the treated patients triggers an alarm.

Initial design:

- 5 patients randomized with active drug and 3 patients randomized with Placebo arm
  - The ratio is 5:3 instead of 2:1 as initially designed
  - The Active arm would be favored for the balance because this would bring the ratio to 6:3, which is aligned with the initially designed 2:1 ratio

Subject	Treatment group	Treatment status	Initial design
1	Active	Treated	Included
2	Active	Treated	Included
3	Placebo	Not Treated	Included
4	Active	Not Continued	Included
5	Placebo	Treated	Included
6	Active	Treated	Included
7	Placebo	Not Treated	Included
8	Active	Pending	Included
9	To be randomized		**Active** favors the balance

- **However,** the patients in the red cells are discontinued or not treated and the sponsor wanted the randomization to only consider the treated patients.

The Solution

Adapting the randomization algorithm

Initial design:

- IDDI RTSM team adapted the randomization algorithm to exclude the patients that are not treated or discontinued and ONLY include the treated patients
- In this case the placebo arm will be favored:
  - Excluding the 3 not treated or discontinued patients => Ratio 4 Active : 1 placebo
  - Adding a placebo => Ratio 4:2 which is the ratio that optimizes the balance. The ratio is 5:3 instead of 2:1 as initially designed

Subject	Treatment group	Treatment status	Initial Design	Initial Design
1	Active	Treated	Included	Included
2	Active	Treated	Included	Included
3	Placebo	Not Treated	Included	Excluded
4	Active	Not Continued	Included	Excluded
5	Placebo	Treated	Included	Included
6	Active	Treated	Included	Included
7	Placebo	Not Treated	Included	Excluded
8	Active	Pending	Included	Included
9	To be randomized		**Active** favors the balance	Placebo favors the balance

Results

- IDDI updated the randomization design in the RTSM system
  - Dynamically exclude the untreated and discontinued patients
  - Possible because of minimization (the solution would not have been possible with a permuted block scenario)

IDDI has successfully delivered

IDDI biostatistics-driven RTSM helped the sponsor to avoid serious imbalance between the two randomized arms for the treated patients

Contact us

Whether you need assistance with your clinical strategy, study design, clinical data management, or biostatistical analysis, IDDI's experts are here to help.

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About IDDI

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We deliver uncompromising excellence in biostatistics, strategic consulting, clinical data management, IDMCs, and supporting eClinical technologies, because when every data point represents a patient, perfection is the only option.