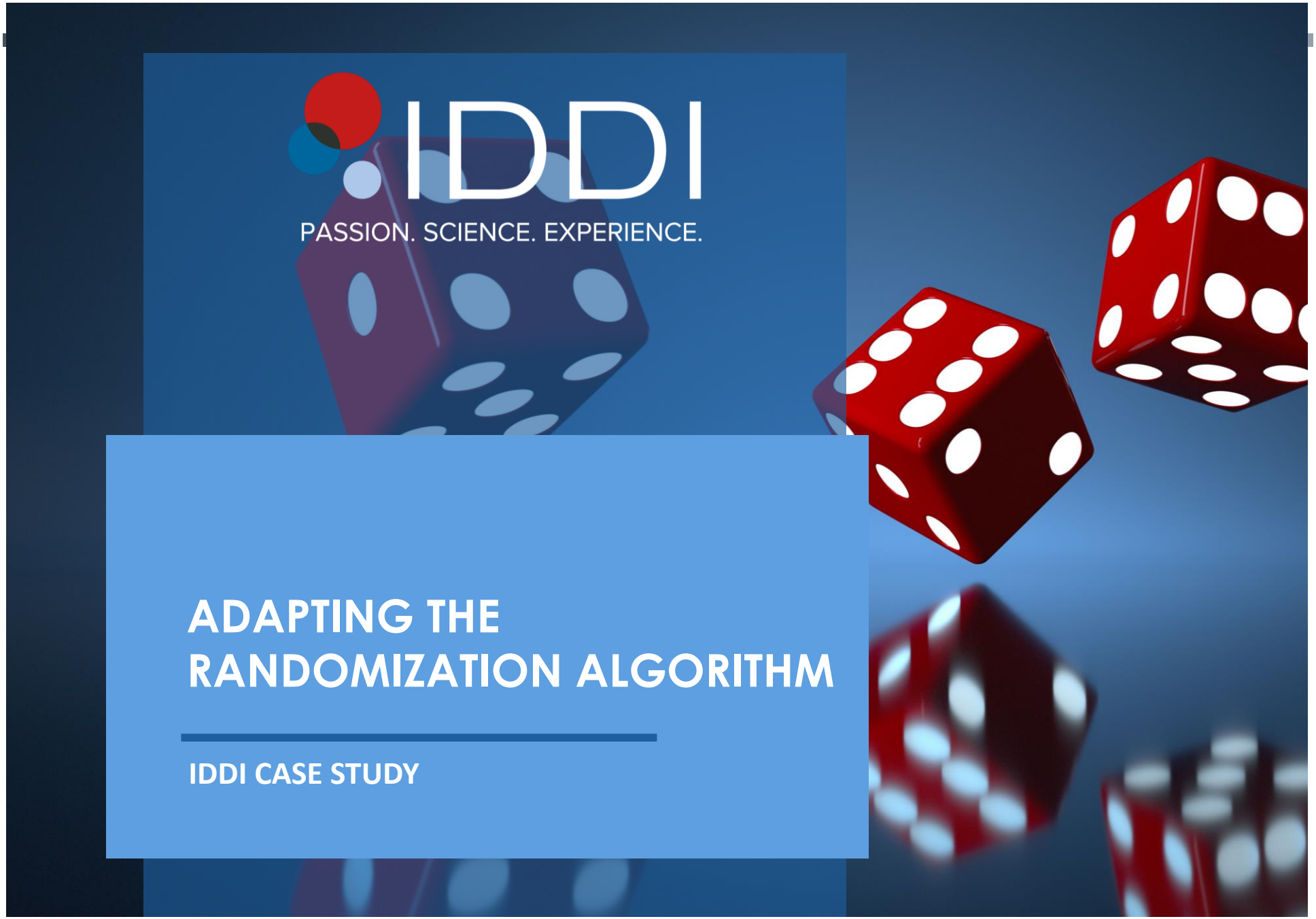
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ADAPTING THE RANDOMIZATION ALGORITHM
IDDI CASE STUDY

STUDY DESCRIPTION

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

INDICATION	PATIENT POPULATION	STUDY DURATION	REGIONS	NO. OF SITES:
Critical Limb Ischemia (CLI)	165 adult subjects	April 2017 – July 2024	North America and Europe	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

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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

- 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

Subject	Treatment group	Treatment status	Initial Design	New 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

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For more information on IDDI's Trial Design - Randomization - Data Management and Biostatistics services for Pharmaceutical and Biotech companies:

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