Zero Loss - ADDPLAN

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CLINICAL
TRIAL

Introduction

Success rate of pharmaceutical (clinical) development

Low success rate of pharmaceutical development

(i) A diminished margin for improvement that escalates the level of difficulty in proving drug benefits.

(ii) Genomics and other new science have not yet reached their full potential.

(iii) Mergers and other business arrangements have decreased candidates.

(iv) Easy targets are the focus as chronic diseases are harder to study, failure rates have not improved.

Critical Path Opportunities List

Innovative adaptive design methods in clinical trials and the potential use of Bayesian approach.

Investigator the flexibility for identifying best (optimal) clinical benefit of the test treatment.

Safety, Futility, Efficacy and Sample size re-estimation.

ADAPTIVE Design

Modify trial and/or statistical procedures -> review of interim data

Efficiently identify clinical benefits of the test treatment
Increase the probability of success of clinical development

Adaptive design is defined as a design that allows adaptations to trial and/or statistical procedures of the trial after its initiation without undermining the validity and integrity of the trial.

Very Attractive

* Reflects medical practice in real world

* Ethical with respect to both efficacy and safety

* Not only flexible, but also efficient in the early and late phase

Types of Adaptive Design

Adaptive Randomization Design

Treatment-Adaptive Randomization

Covariate-Adaptive Randomization

Response-Adaptive Randomization

Group Sequential Design

Prematurely stopping a trial due to safety, futility/efficacy

Control the overall type I error rate

Desired level of 5%

Sample Size Re-estimation Design

Based on the observed data at interim

Treatment Effects

Conditional Power

Reproducibility Probability

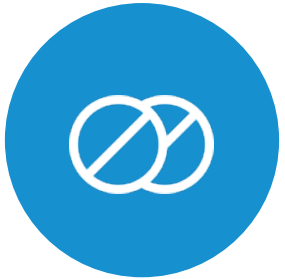
Adaptive Dose Finding

Early Phase

MED / MTD

Continual Re-assessment Method

(CRM)



Drop-the-Loser Design

Inferior Treatment Groups

Phase II

Precision Analysis

Types of Adaptive Design

Biomarker-Adaptive Design

Select Right Patient Population

Identify Nature Course of Disease

Early Detection of Disease

Adaptive Treatment-Switching Design

Initial to Alternative

Lack of Efficacy or Safety

Estimation of Survival

Hypothesis-Adaptive Design

Database Lock and/or Prior to Data Unblinding

Superiority Hypothesis

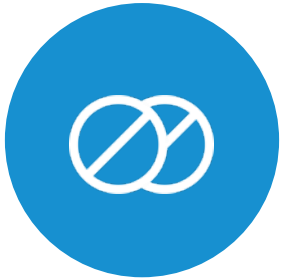
Clinical and Statistical Justifiable

Adaptive Seamless Phase II/III Trial Design

Data from Patients Enrolled Before/After

Two Stage Design

Validity and Efficiency



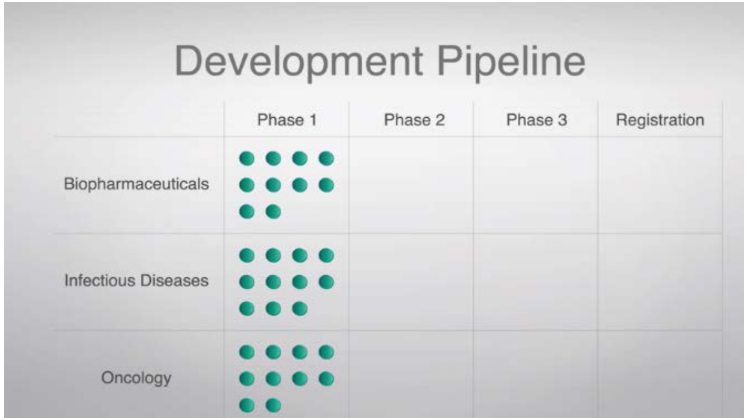
Multiple Adaptive Design

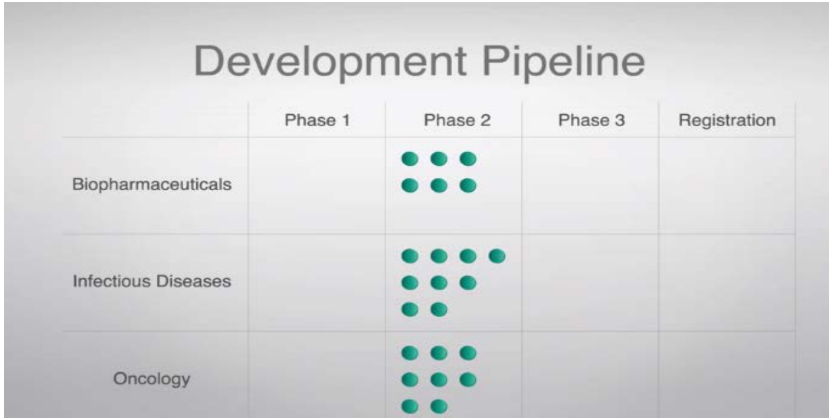
Any Combinations

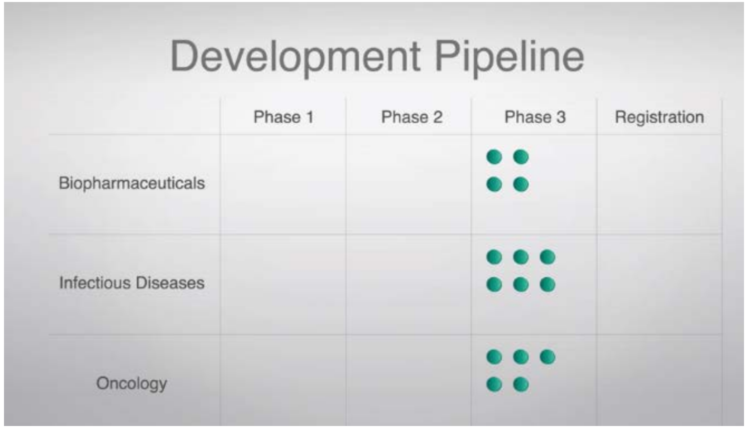
Clinical Trial Simulation

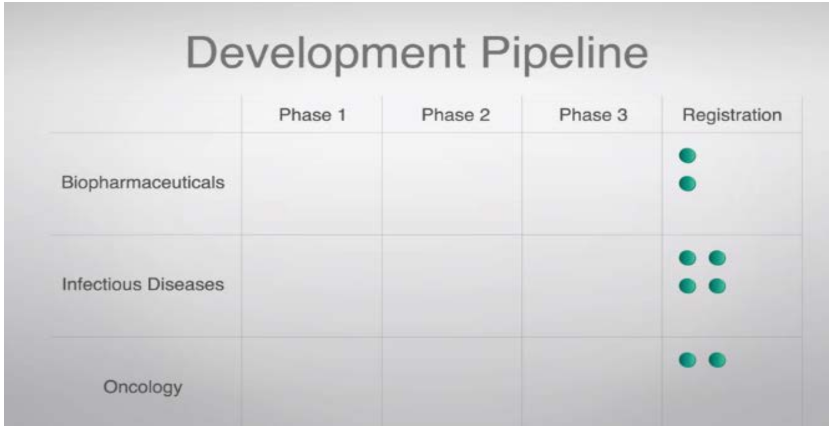
Planning Stage

Development Phase









THERE'S A BETTER WAY

ADDPLAN

ADDPLAN® is a stand-alone software, using data to design, simulate, and analyze adaptive clinical trials with ease.

Market leader for design, simulation and analysis of adaptive clinical trials
Spans Phases I to IV

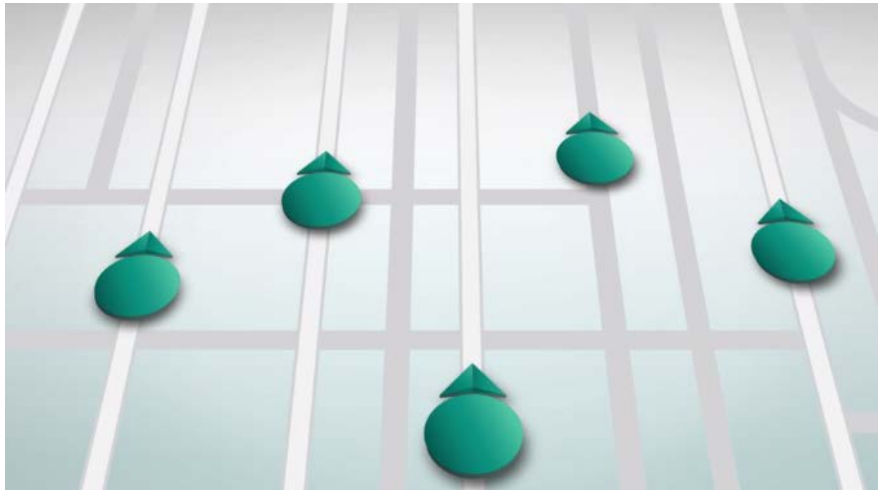
Used by regulatory agencies (FDA, EMA (Europe) and PMDA (Japan), top pharmaceuticals, medical device companies, and academia
The only commercial software with MCP-Mod dose finding methodology
MCP-Mod has recently received FDA endorsement2 and EMA qualification1

ADDPLAN® is a fully validated, graphical user interface (GUI) based software.

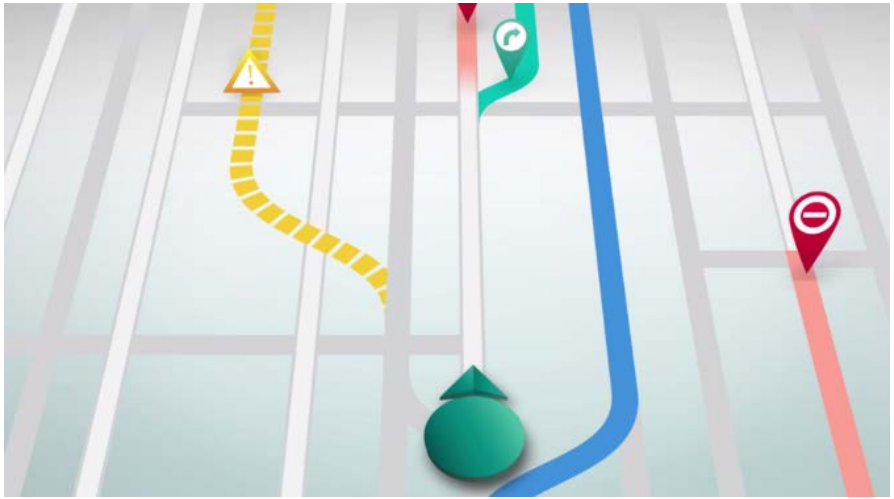
ADDPLAN® functionality covers innovative study designs for all phases of clinical development:

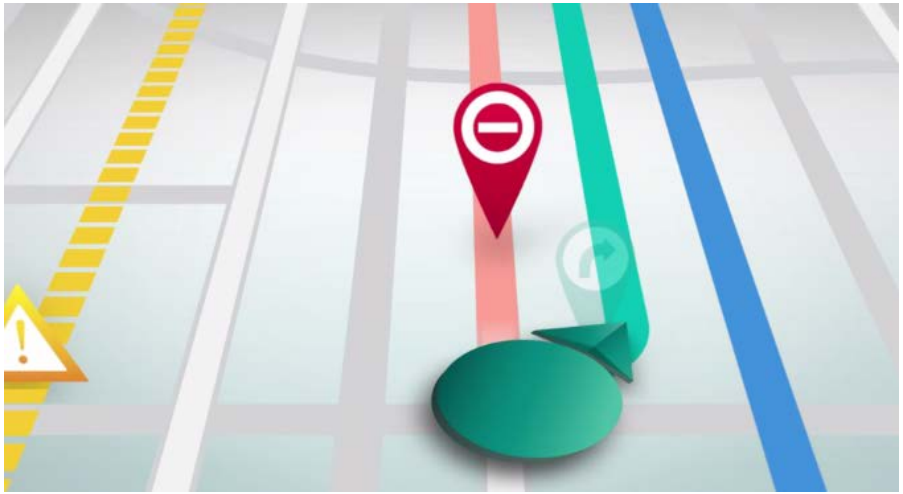
Under ADDPLAN BASE

* Early stopping for efficacy
* Binding and non-binding stopping for futility

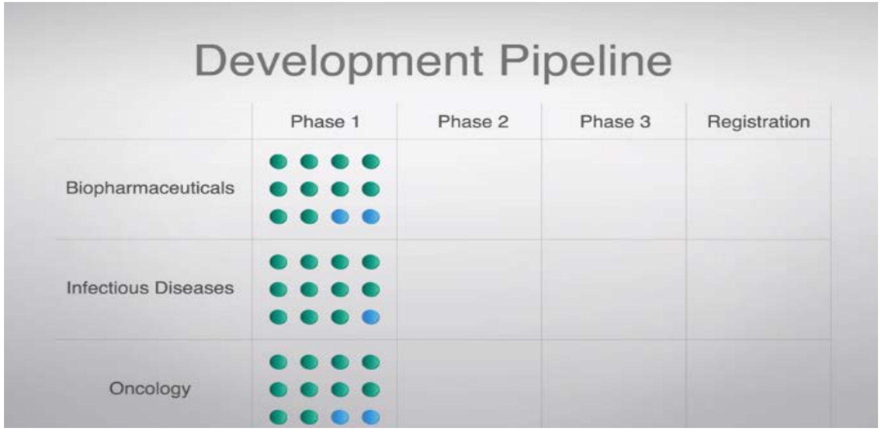


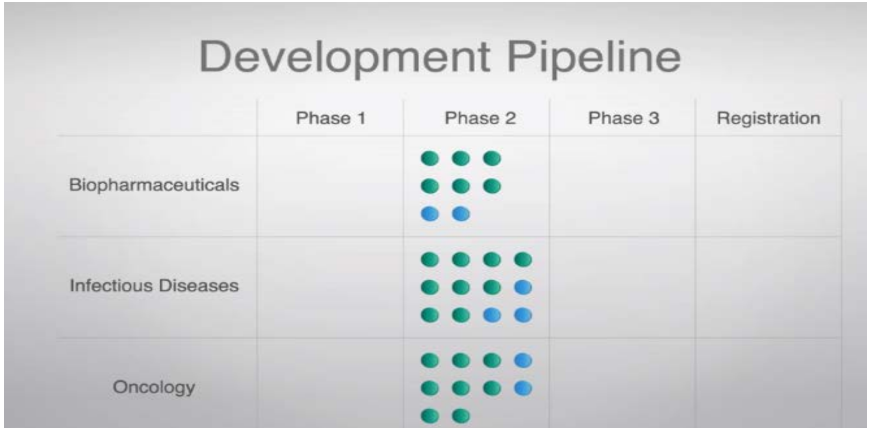

Unexpected Toxicity
or Inadequate Efficacy

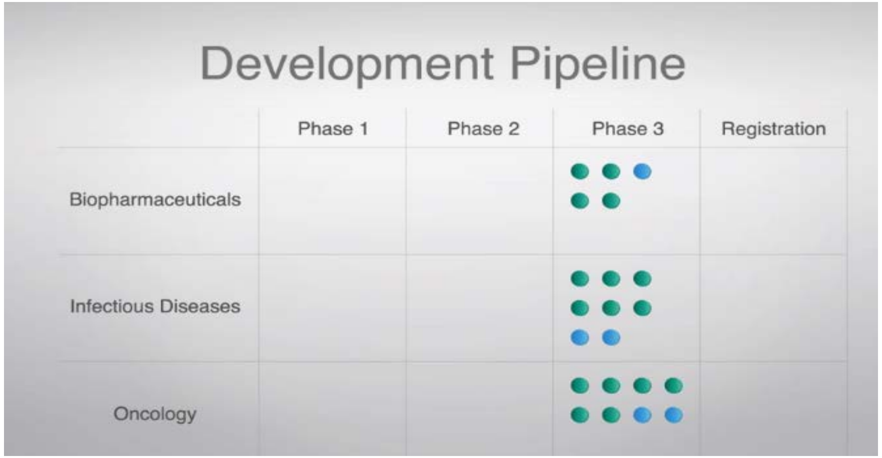


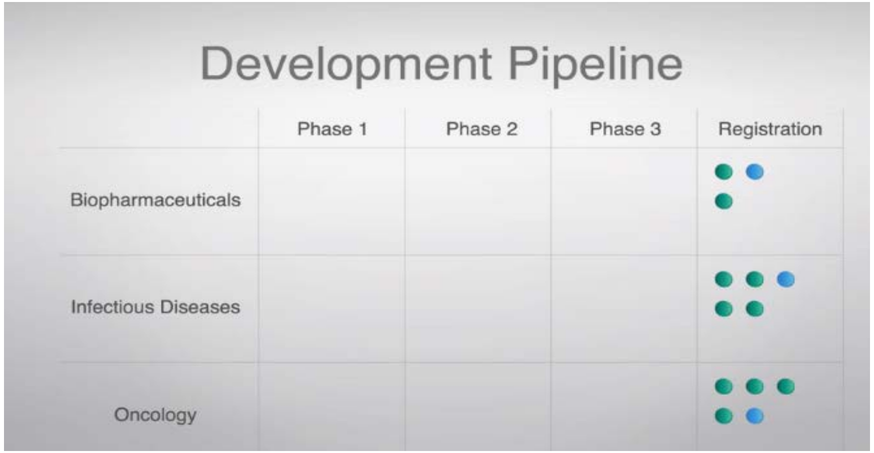


ADDPLAN Intiation

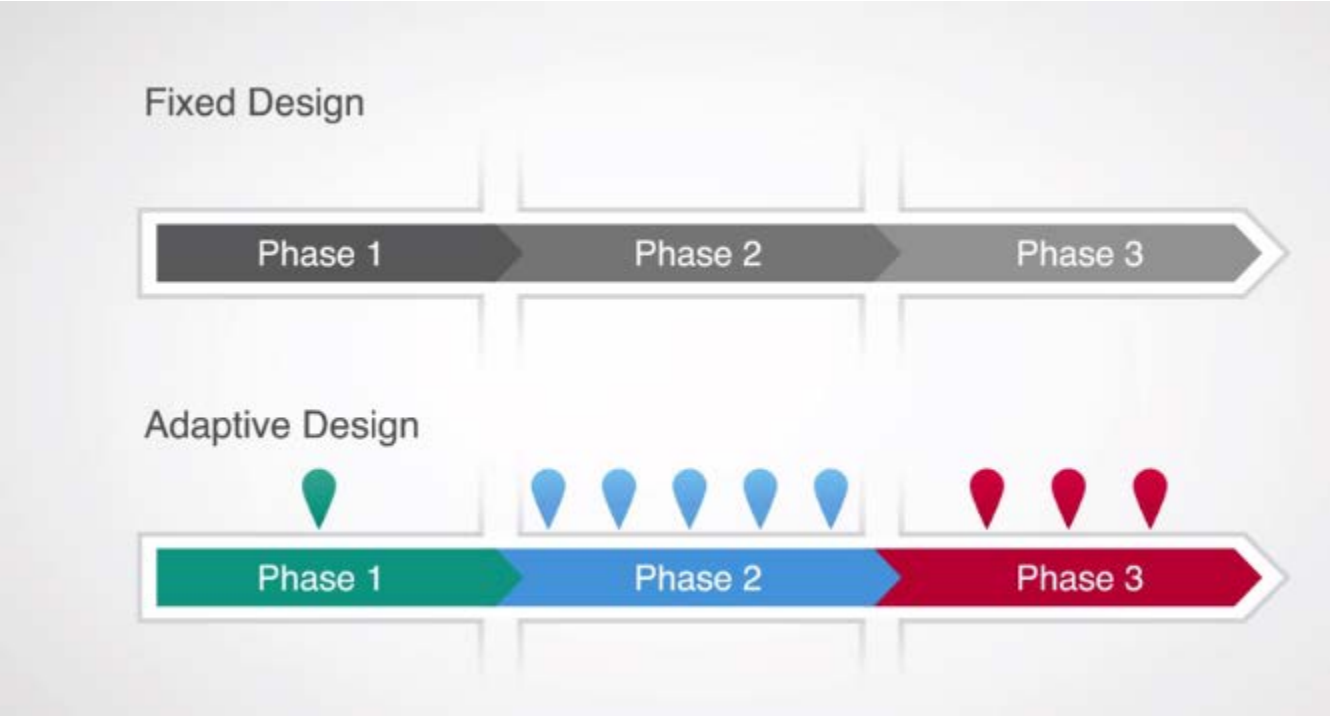


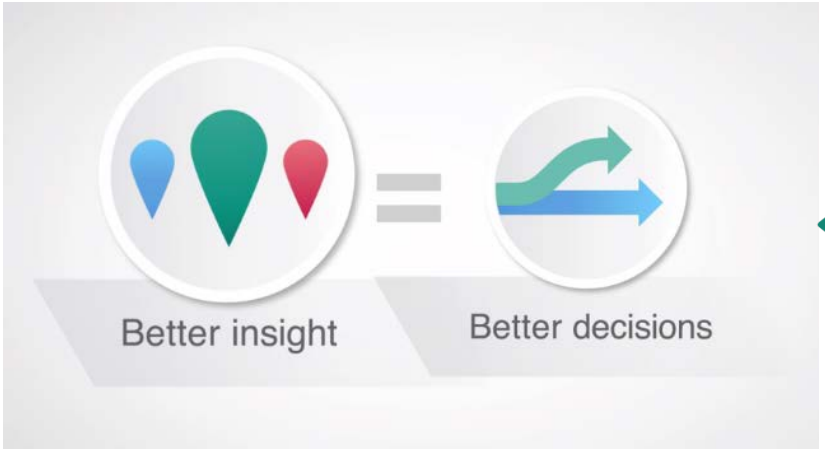


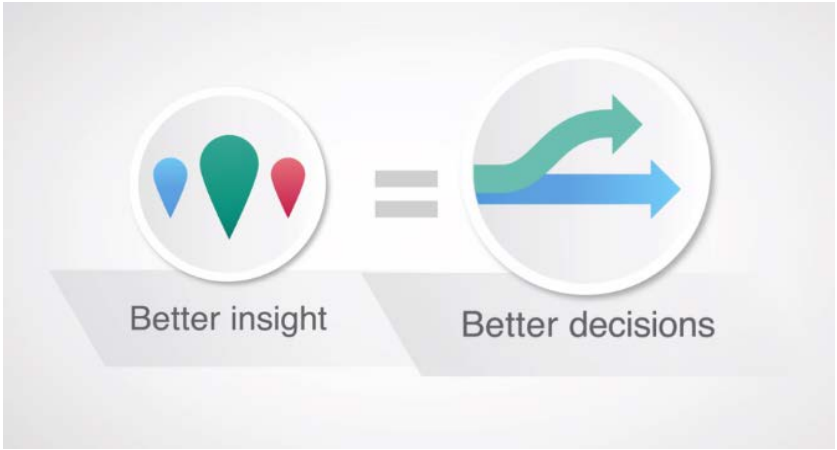




Comparison

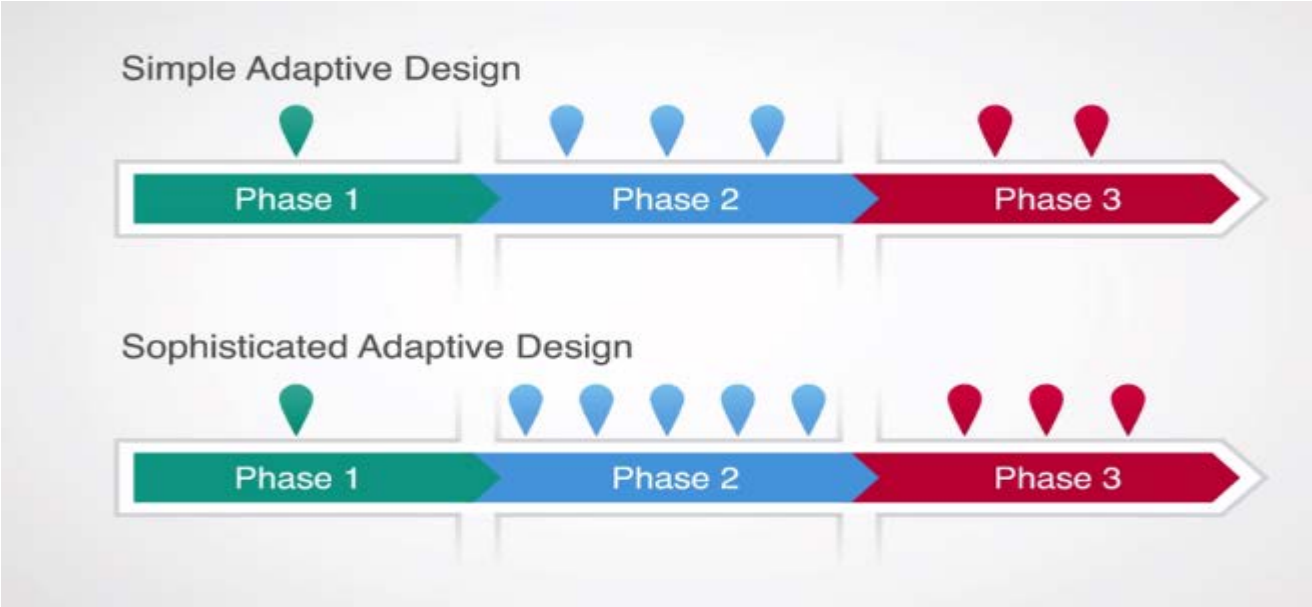

Fixed Design
Phase 1
Phase 2
Phase 3
Adaptive Design
Phase 1
Phase 2
Phase 3


Better insight
Better decisions

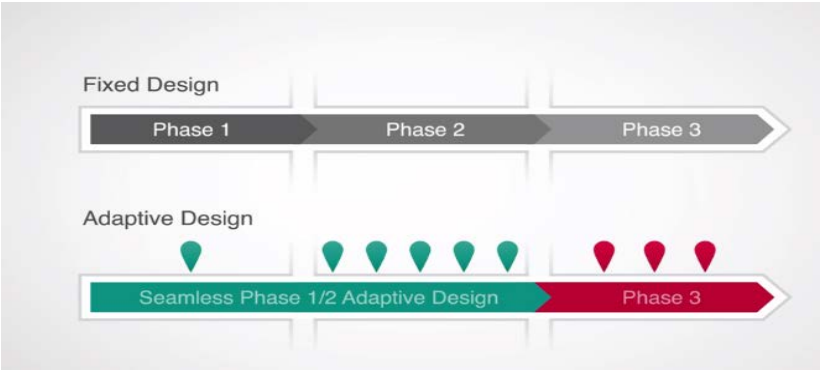

Better insight
Better decisions

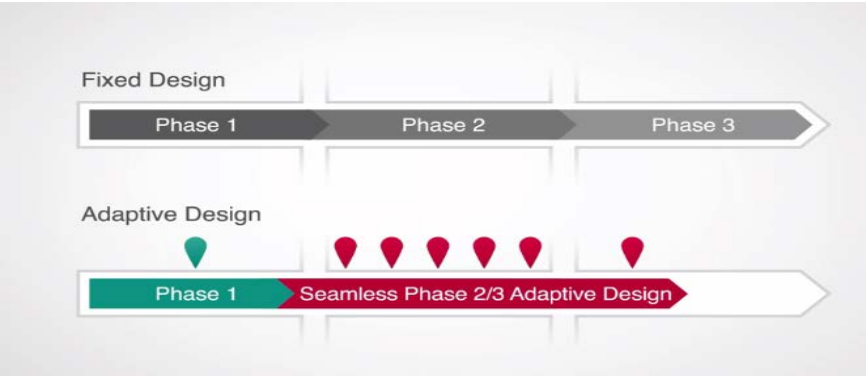
- Dose Escalation
- Sample Size re-estimation
- Early Trial Termination

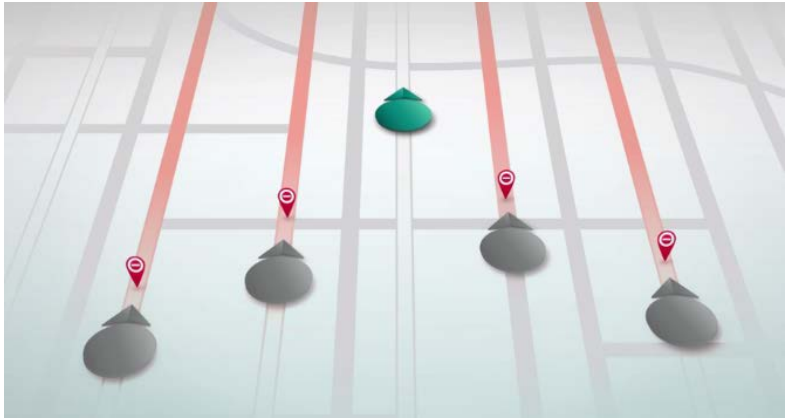
Simple Vs Sophisticated Design

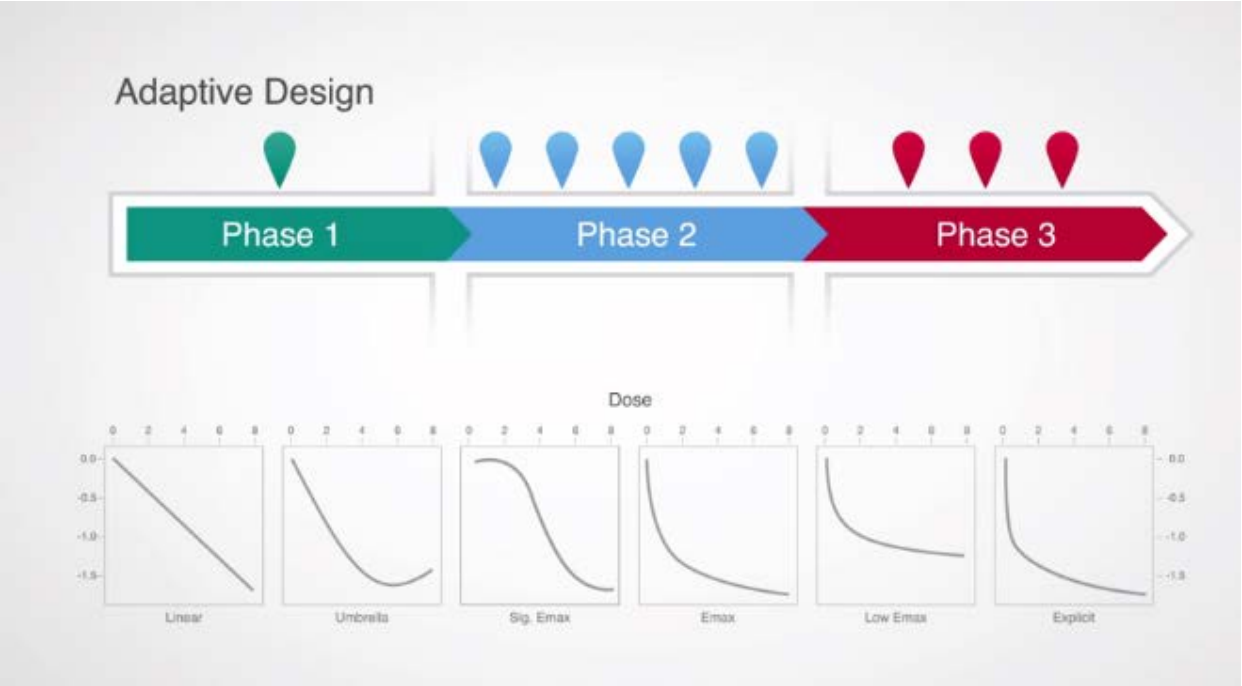


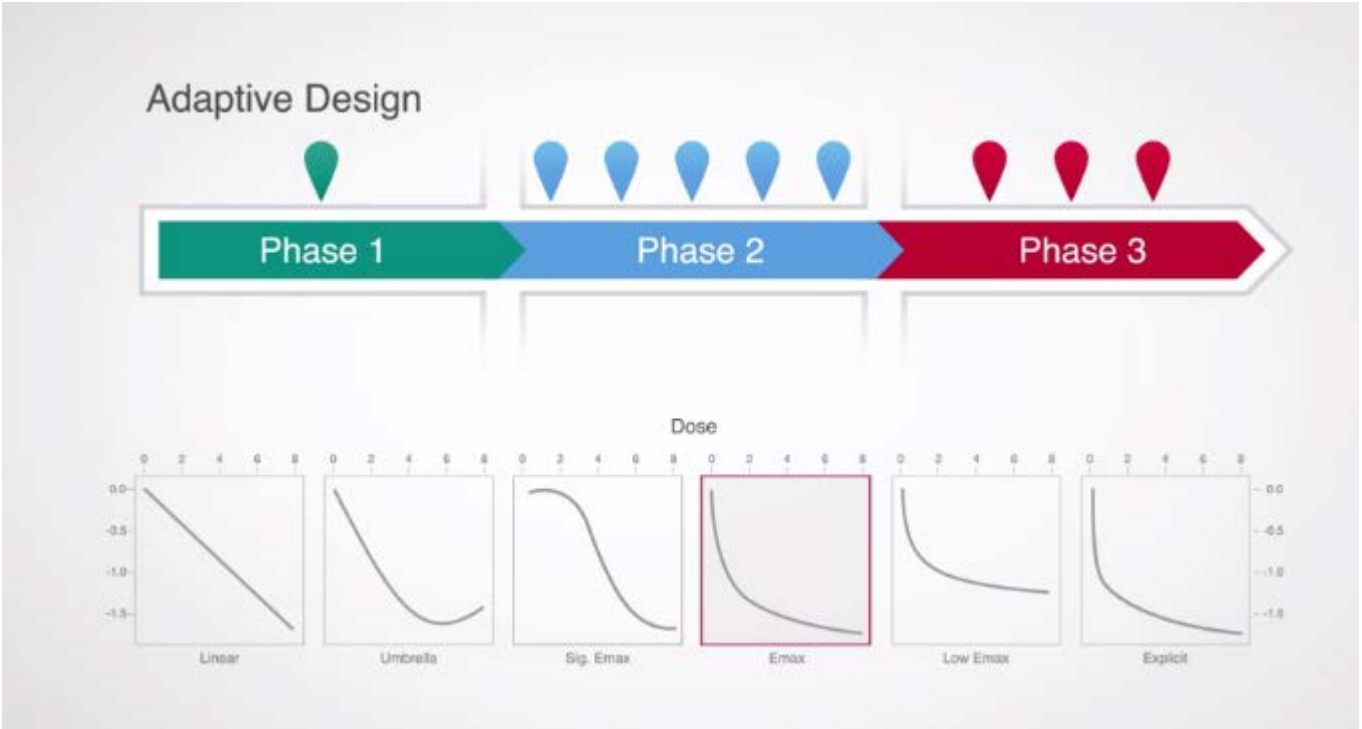
- Additional or Removal of Dose Groups
- Enrichment of Specific Patient Population

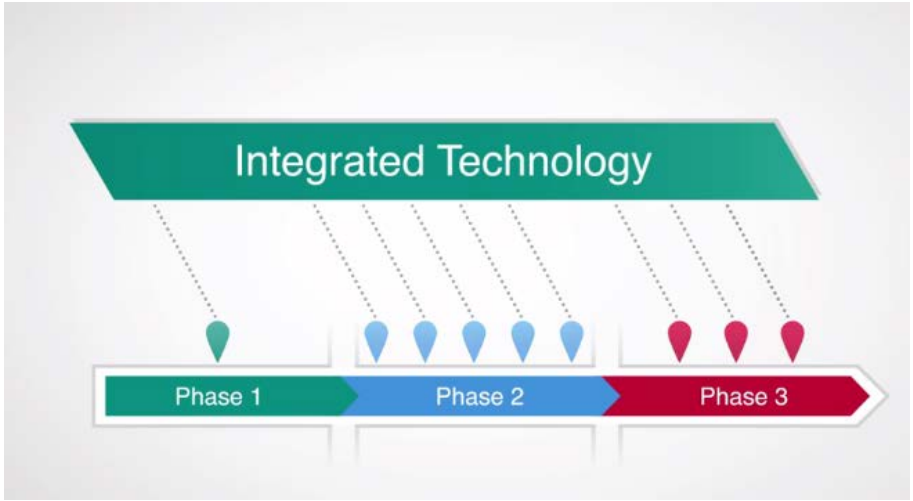

Fixed Design
Phase 1
Phase 2
Phase 3
Adaptive Design
Seamless Phase 1/2 Adaptive Design
Phase 3


Fixed Design
Phase 1
Phase 2
Phase 3
Adaptive Design
Phase 1
Seamless Phase 2/3 Adaptive Design




Adaptive Design
Phase 1
Phase 2
Phase 3
Dose
Linear
Umbrella
Sig. Emax
Emax
Low Emax
Explicit


Adaptive Design
Phase 1
Phase 2
Phase 3
Dose
Linear
Umbrella
Sig. Emax
Emax
Low Emax
Explicit



Integrated Technology

Integrated EDC

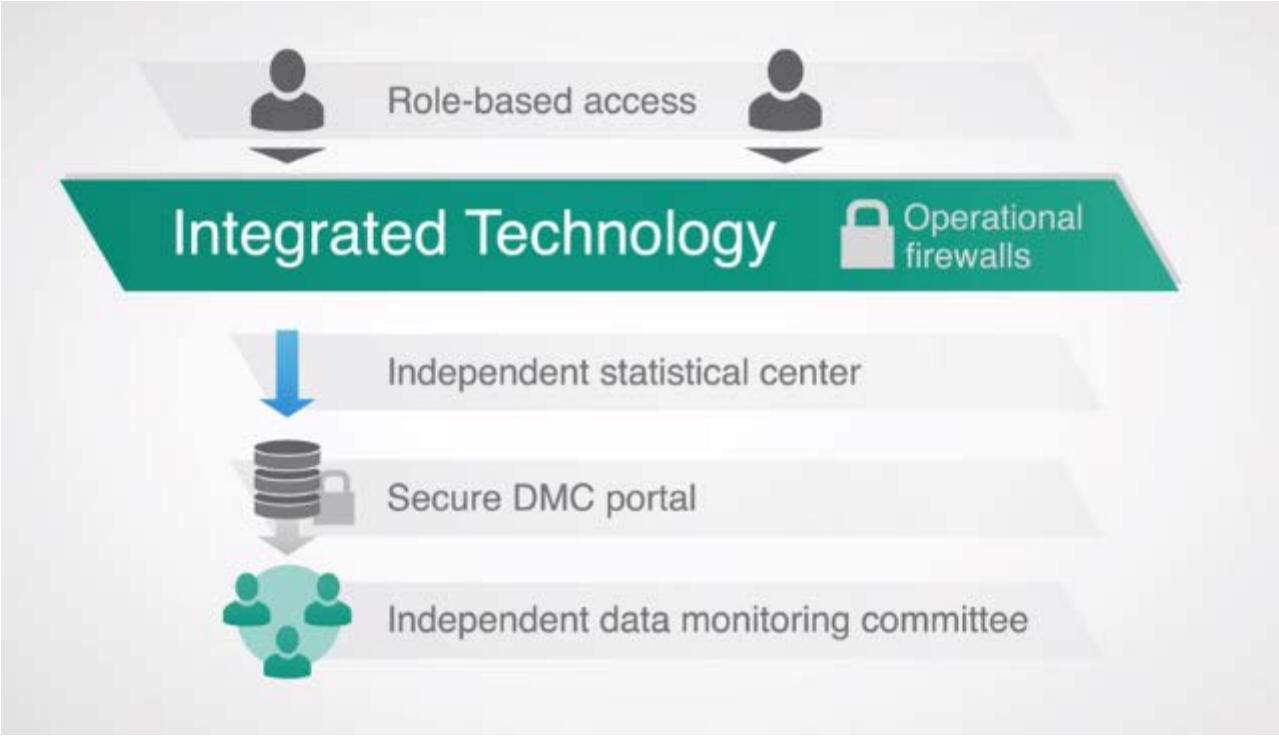
Randomization

Drug Supply Management

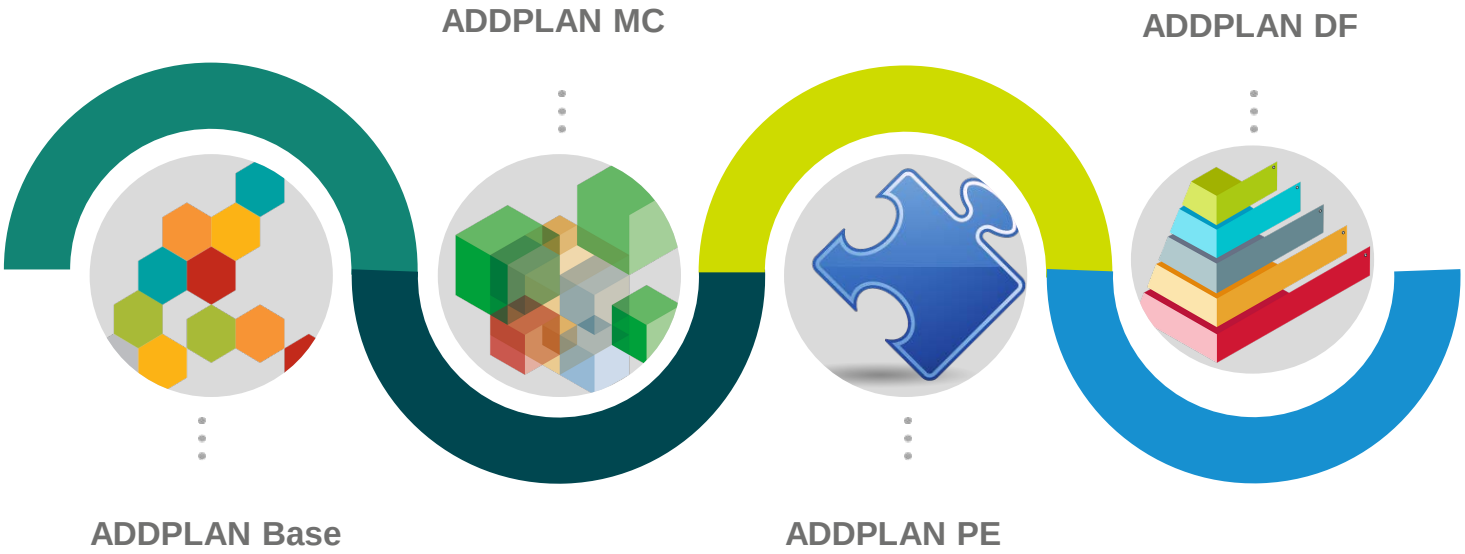
Integrated Technology ➡ Instream data Cleaning

➡ Interim Analyses ready all time

➡ Efficient, Timely Delivery of Data


Role-based access
Integrated Technology
Operational firewalls
Independent statistical center
Secure DMC portal
Independent data monitoring committee

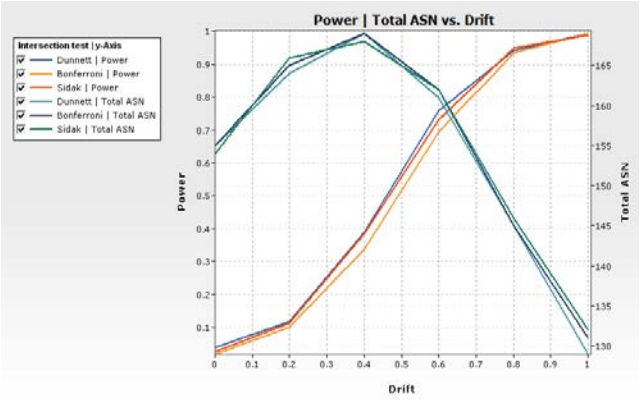
ADDPLAN® Modules



ADDPLAN Base

- ADDPLAN® BASE was the first validated adaptive group sequential design software including
- Study types: Superiority, Non-inferiority and Equivalence testing

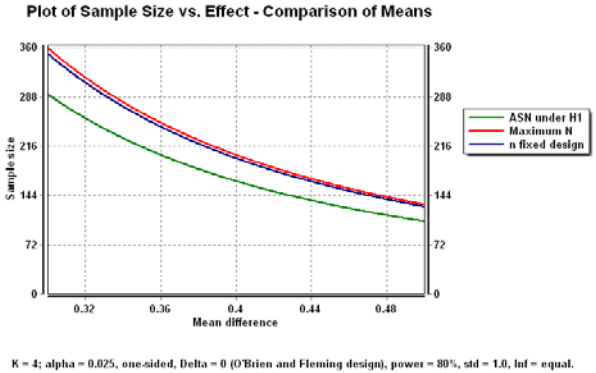
- **Plan New Design:** Sample size and power calculations
- **Simulate Design**: Calculation of operating characteristics for adaptive group sequential designs
  - Sample size re-estimation
  - Considering the interim effect estimator or originally assumed effects
  - Control of false positive rate guaranteed
  - Higher flexibility in sample size re-estimation
- **Adaptive Analysis**:
  - Decision recommendations
  - Sample size re-estimation
  - Conditional power calculation - total sample size
  - Repeated confidence intervals
  - Re-planning



ADDPLAN MC

ADDPLAN® → Multi-armed study design

Simulate Design: Simulation of inferentially & operationally seamless Phase II/III designs



#Control of family-wise error rate

1. Early success/futility stopping
2. Sample size re-estimation based on conditional power

→ Adaptive treatment arm selection
→ Wide range of treatment arm selection rules
→ Sample size re-estimation
→ Different dose-response profiles
→ Simulation of treatment selection based on surrogate endpoints for survival data

Adaptive Analysis: Interim & final analysis of adaptive multi armed study designs

→ Flexible dropping
→ Sample size re-estimation

→ Conditional power calculation based on the remaining total sample size
→ Repeated confidence intervals taking possible early stopping into account.

ADDPLAN PE

ADDPLAN® PE

→ Population Enrichment

→ Sub population Designs

Simulate Design:

→ Wide range of subgroup (population) selection rules

→ Simulation of population - surrogate endpoints for survival data

→ Simulation of treatment - surrogate endpoints for survival data

Adaptive Analysis:

→ Repeated confidence intervals taking possible early stopping into account.

ADDPLAN DF

ADDPLAN® DF - Multiple Comparison Procedure and Modeling (MCPMod) approach.

Poor **Q**uality **L**earning - **E**arly **P**hase of **D**rug **D**evelopment - Attrition.

→ Improved dose selection

→ Phase I and Phase - Efficiency and Effectiveness.

→ Optimum Experimental Design.

→ Combination of data from different dose levels

→ Insight into the underlying dose-response relation

Procedures for MCPMod, classical dose-response modelling and signal testing:

→ Functionality

→ Model-based trend tests in dose finding

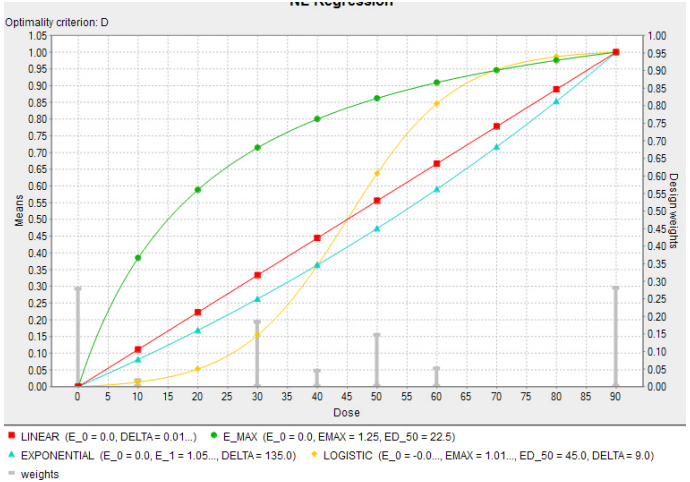
ADDPLAN DF

Design optimization:

→ Selection of most informative study doses
→ Efficiency calculation: Comparison of candidate designs to optimal designs
→ Precision of Dose Estimation - Probability of Correct Model Selection - Modelling Precision - Success Probability

Analysis functionality conducting:

→ Trend tests
→ Frequentistic/Bayesian/Bootstrap Modelling
→ Dose estimation & prediction
→ Dose Escalation Designs
→ Recruitment modelling



Reference:
https://www.ncbi.nlm.nih.gov

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Thank you

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