

EnForeSys - an Advanced Patient Enrollment Forecaster with Monte Carlo Simulations

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Clinical Trials - Challenges



Planning Solutions

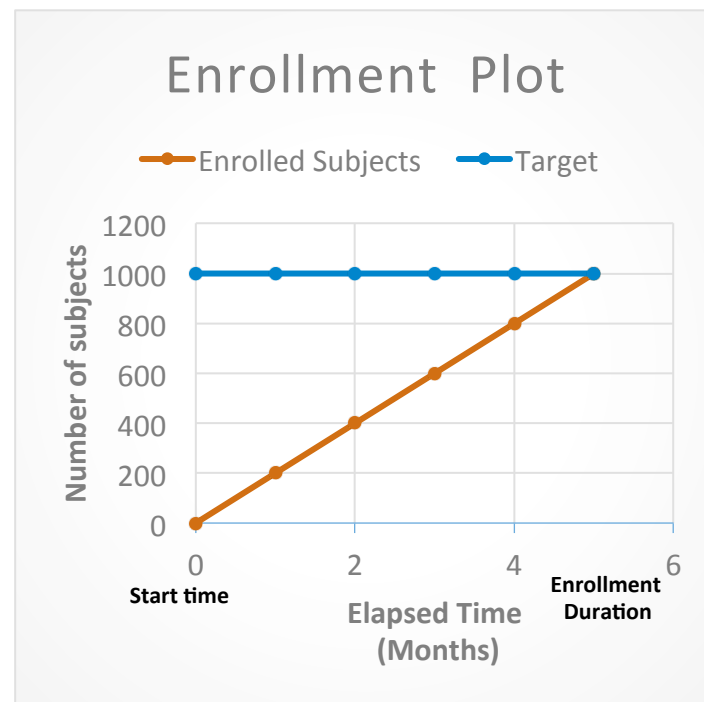
- **Straight Line Projections**

Assumptions:

- All sites get ready at the start of the trial
- No site fails to recruit
- Subjects arrive at a constant rate
- No pause for Interim Analysis

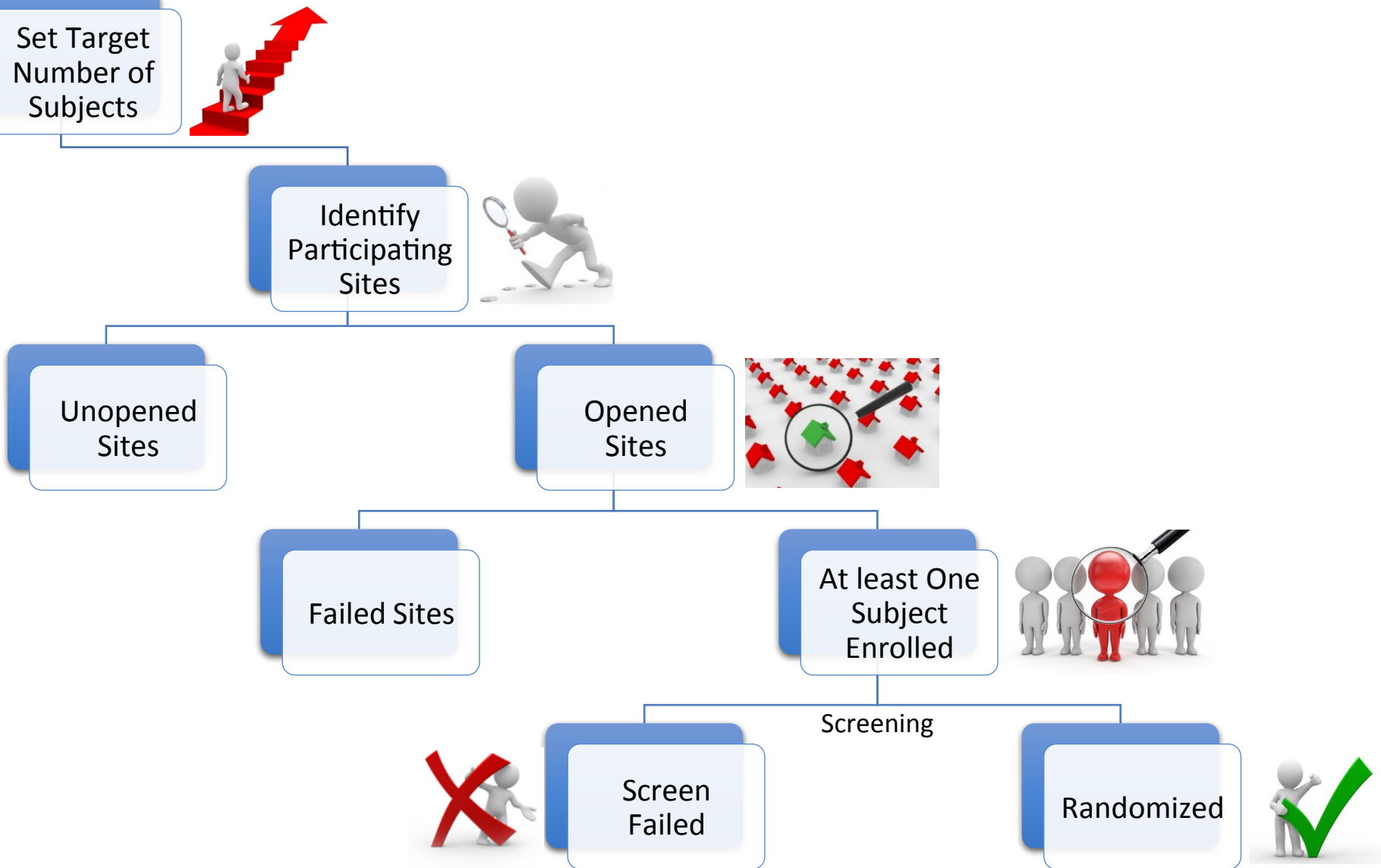
- **Simulations**

- Considers uncertainties in real world scenarios
- Accrual rate is not uniform
- Involves complex computation



- **Enrollment Forecasting System**
- Software to simulate clinical trial enrollment
- Uses Monte Carlo Simulations
- Computes trial duration using the site and recruitment information.
- Factors impacting clinical trial enrollment:
 - Number of countries /sites
 - Site initiation time
 - Screening rates
 - Screen and site failure rates

Steps in Enrollment Process



Case Study

- Impova - drug aimed at alleviating the symptoms of seasonal allergies.
- Efficacy established in phase II trials
- Undergo phase III trial - for safety and efficacy
- To be tested on 700 subjects for a trial beginning on 1st January, 2017
- Subjects enrolled in multiple sites across ten countries

Inputs

Site Inputs

Plan Recruitment

Group Sites By: Country

Number of Countries: 10

Distribution of Site Initiation Visit Time: Uniform

Distribution of Max. # of Subjects Randomized: Fixed

[Import Site Info...](#)

Site Initiation Visit Time Input Type: ☒ Interval ☐ Date

Site Initiation Visit Time Unit: Months

Site Performance Threshold
(# of Randomizations)

Low: 2

High: 9

☒ Include Site Failure Effect

Distribution of Site Failure: Binomial

Failure Probability: 0.1

Country	# of Sites	Site Initiation Visit Time		Max. # of Subjects Randomized
		Minimum	Maximum	
Austria	9	9	11	70
Belgium	13	11	13	118
Canada	11	7	12	700
France	17	7	12	128
Germany	18	8	13	85

Inputs

Recruitment Inputs

Target Randomization: Randomization Duration:

Recruitment Model: Poisson

Input Rate:

Distribution of Randomization Rate: Gamma

Gamma Input:

Randomization Rate Time Unit:

☒ Include Screening Failure Effect

Screening Period:

Distribution of Screening Failure Prob.: Fixed

Failure Probability:

Country	# of Sites	Randomization Rate/Site	
		Mean	Std. Dev.
Austria	9	0.49	0.28
Belgium	13	0.49	0.28
Canada	11	0.31	0.18
France	17	0.48	0.28
Germany	18	0.59	0.34

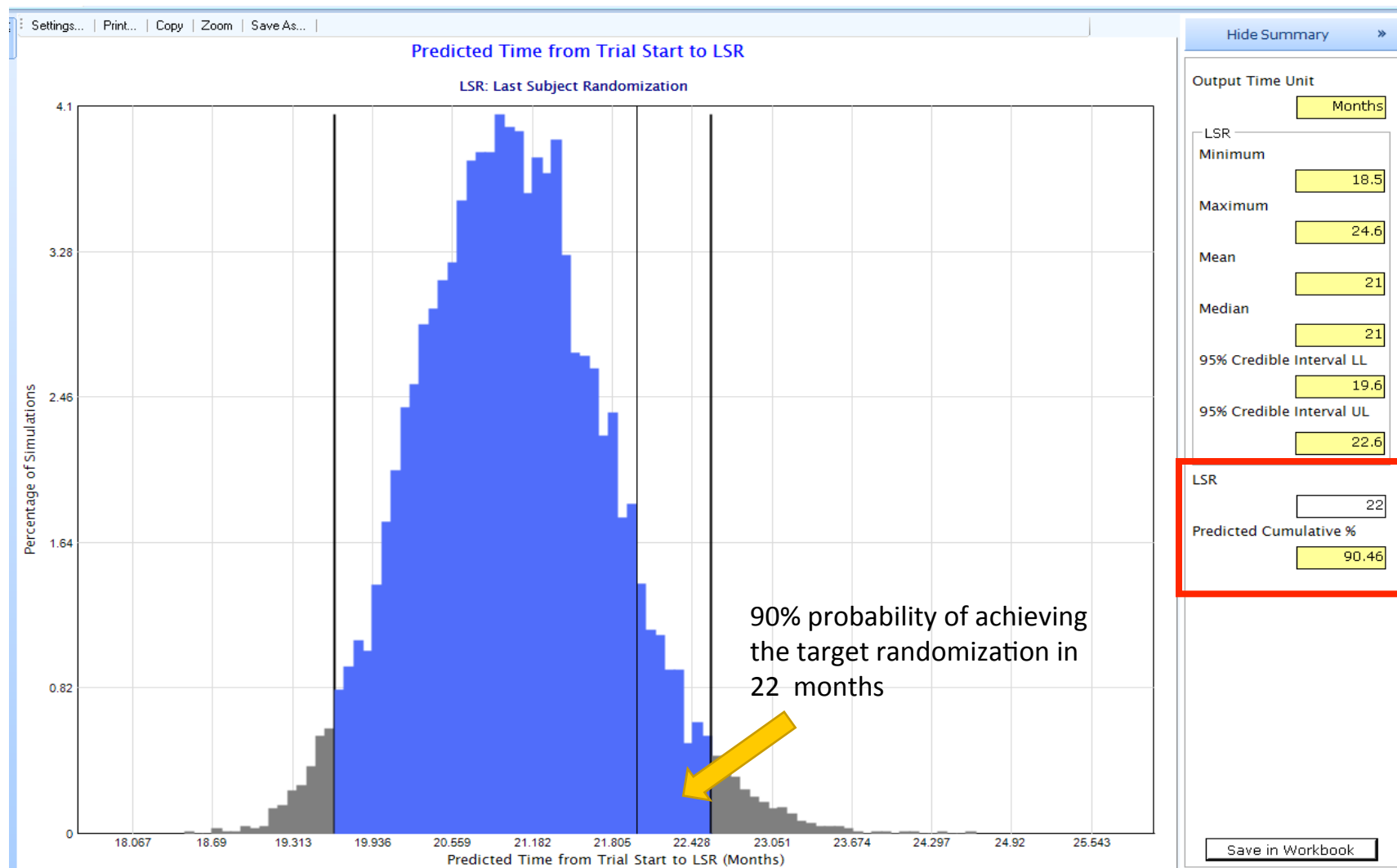
Scenario 1

- Screen and site failure rates - not considered

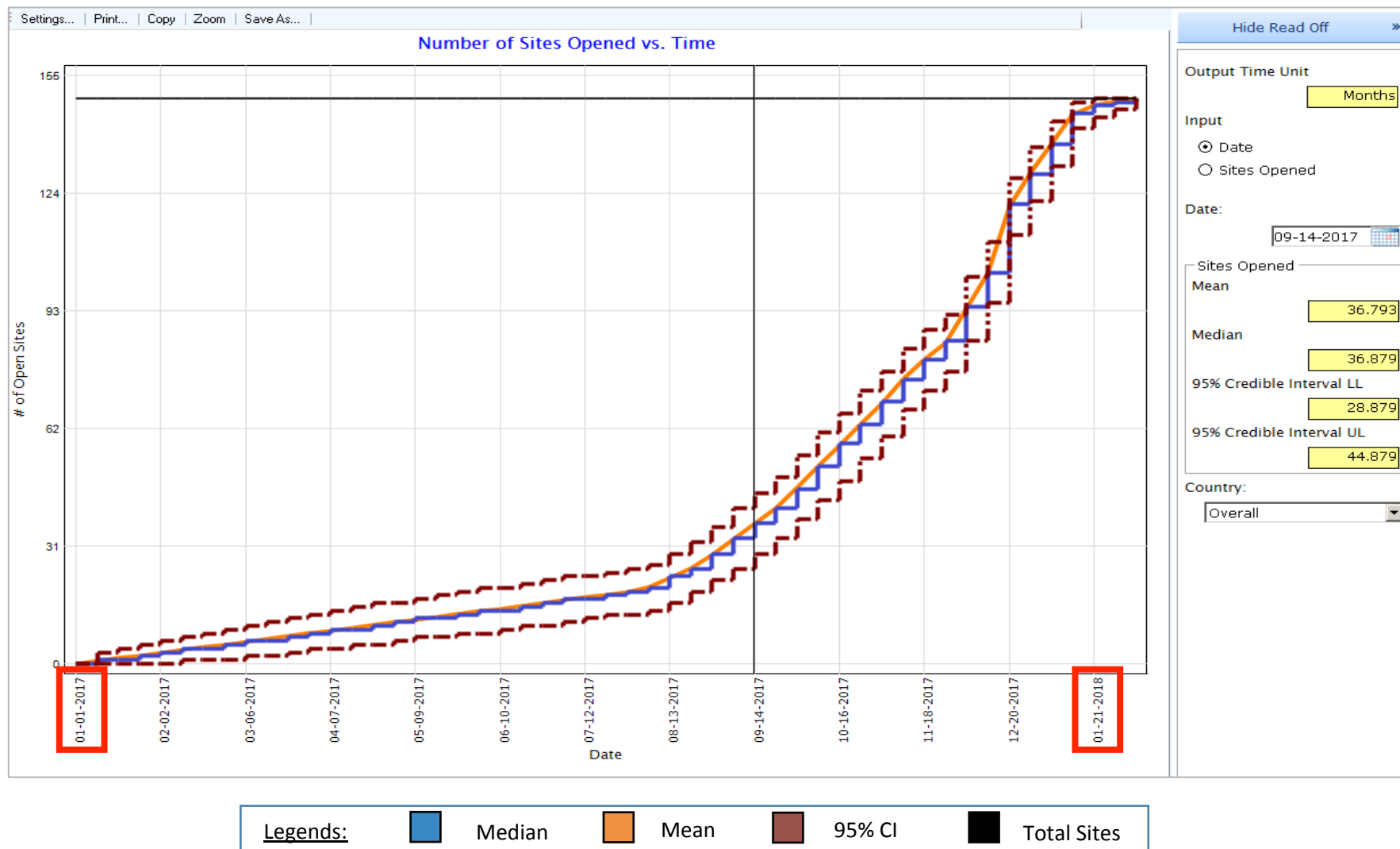
Wbk2:Scenario 1	
Trial Details	
Group Sites By	Country
# of Groups	10
Total # of Sites	149
Plan	
Target Randomization	700
Ramp Up Factor	1
Site Information	
Distribution of Site Initiation Time	Uniform
Max # of Subjects Distribution	Fixed
Recruitment Information	
Recruitment Model	Poisson
Distribution of Randomization Rate	Gamma
Randomization Rate Time Unit	Months
Simulation Results (Overall)	
Mean Time from Trial Start to FSR	1.6
Mean Time from Trial Start to FSIV	0.4
Mean Time from Trial Start to LSR	21
Mean # of Sites Opened	149
Mean # of Subjects Screened per Site	4.7
Mean # of Screen Failures	0
Mean # of Sites with at least 1 Subject Screened	139.333
Mean Randomization Rate/Site	0.423
Output Time Unit	Months

← Overall Trial Duration

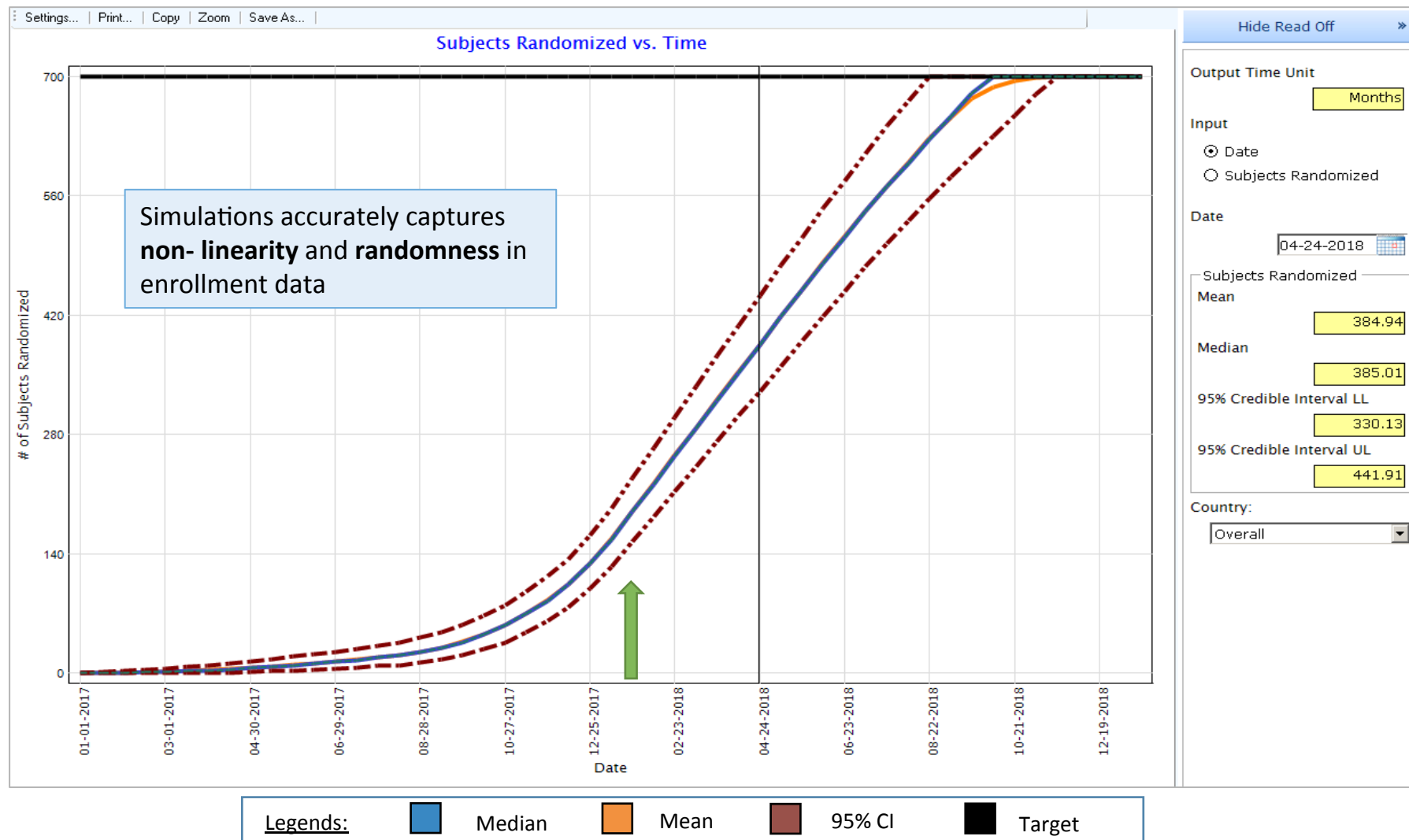
Scenario 1



Scenario 1



Scenario 1



Scenario 1

Site Performance Summary

# of Rand.	# of Sites					
	Mean	Median	25th %ile	75th %ile	95% Credible Interval	
					LL	UL
0-2	46.546	46	44	49	38	55
3-8	81.891	82	78	86	70	94
>=9	20.563	21	19	22	15	26

Country Wise Recruitment Summary (Mean)

Country	# of Sites Opened	FSIV (Months)	# of Subjects		Screening Rate/Site (Subjects/Site/Month)	Rand. Rate/Site (Subjects/Site/Month)
			Screened	Randomized		
Austria	9	8.9	50.271	50.271	0.492	0.492
Belgium	13	10.9	59.468	59.468	0.49	0.49
Canada	11	7.4	39.441	39.441	0.31	0.31
France	17	7.3	94.636	94.636	0.48	0.48
Germany	18	8	84.638	84.638	0.596	0.596
Netherlands	8	11.4	38.317	38.317	0.538	0.538
Russia	17	10.9	101.753	101.753	0.641	0.641
Sweden	8	7.9	37.462	37.462	0.39	0.39
UK	13	10.3	50.285	50.285	0.411	0.411
USA	35	0.4	143.729	143.729	0.281	0.281

Scenario 2

- Trial duration = 18 months

	Wbk1:Scenario 1	Wbk1:Scenario 2
Trial Details		
Group Sites By	Country	Country
# of Groups	10	10
Total # of Sites	149	149
Plan		
Target Randomization	700	700
# of Interim Analyses	1	1
Interim Analysis Duration	15	15
Screening Rates Multiplier During IA	0.75	0.75
Randomization Duration		18
Ramp Up Factor	1	
Site Information		
Distribution of Site Initiation Time	Uniform	Uniform
Max # of Subjects Distribution	Fixed	Fixed
Recruitment Information		
Recruitment Model	Poisson	Poisson
Distribution of Randomization Rate	Gamma	Gamma
Randomization Rate Time Unit	Months	Months
Simulation Results (Overall)		
Mean Time from Trial Start to FSR	1.6	1.4
Mean Time from Trial Start to FSIV	0.4	0.3
Mean Time from Trial Start to LSR	21	18
Mean # of Sites Opened	149	149
Mean # of Subjects Screened per Site	4.7	4.7
Mean # of Screen Failures	0	0
Mean # of Sites with at least 1 Subject Screened	139.333	139.048
Mean Randomization Rate/Site	0.423	0.572
Computed Ramp Up Factor		1.372
Output Time Unit	Months	Months

← Estimated Ramp-up factor

Scenario 3

- Site failure rate = 0.1 & Screen failure rate = 0.2

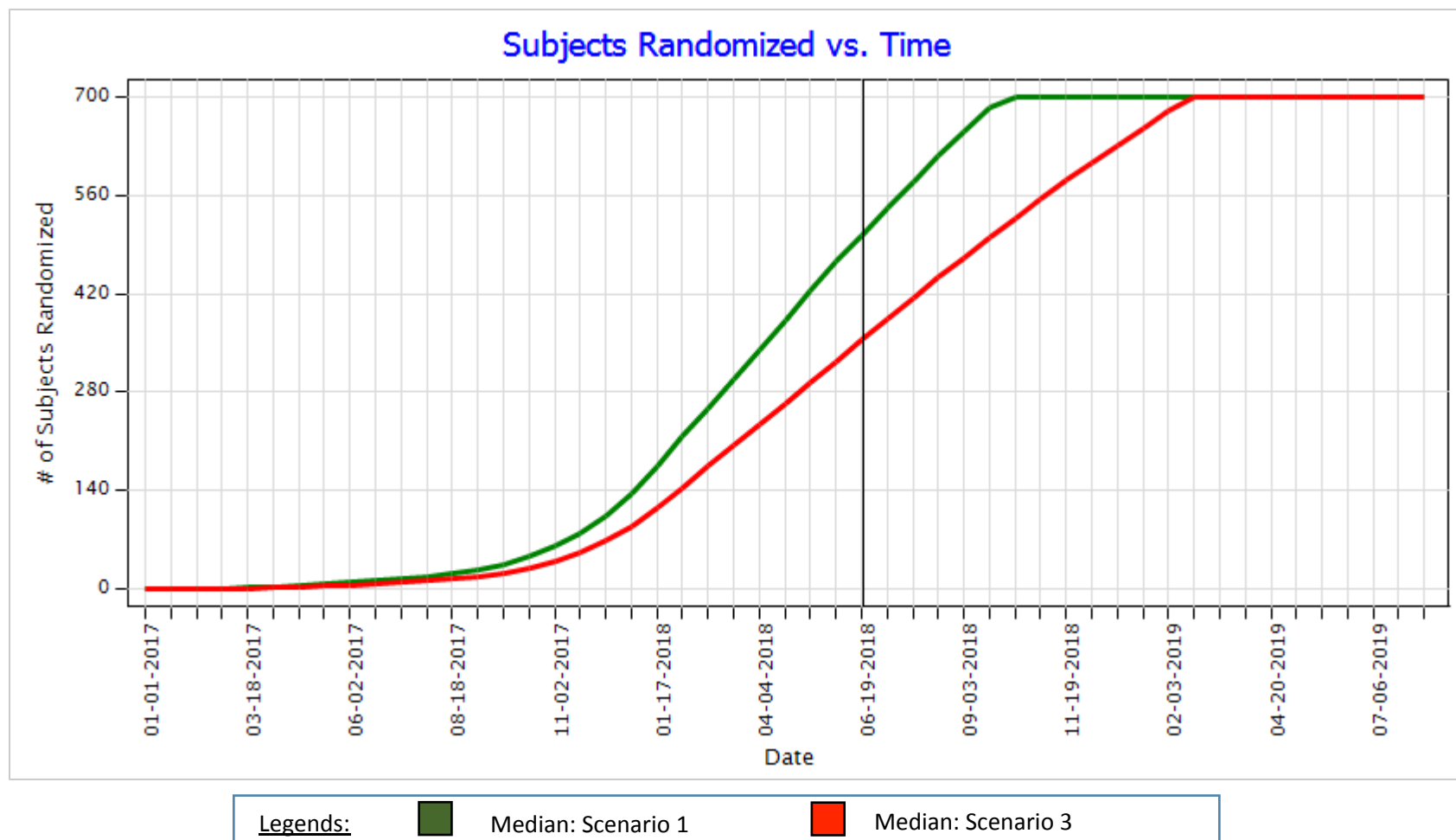
	Wbk1:Scenario 1	Wbk1:Scenario 3
Trial Details		
Group Sites By	Country	Country
# of Groups	10	10
Total # of Sites	149	149
Plan		
Target Randomization	700	700
# of Interim Analyses	1	
Interim Analysis Duration	15	
Screening Rates Multiplier During IA	0.75	
Ramp Up Factor	1	1
Site Information		
Distribution of Site Initiation Time	Uniform	Uniform
Max # of Subjects Distribution	Fixed	Fixed
Distribution of Site Failure		Binomial (0.1)
Recruitment Information		
Recruitment Model	Poisson	Poisson
Distribution of Screening Rate		Gamma
Distribution of Randomization Rate	Gamma	
Screening Rate Time Unit		Months
Randomization Rate Time Unit	Months	
Distribution of Screening Failure Rate		Fixed (0.2)
Screening Period		1
Simulation Results (Overall)		
Mean Time from Trial Start to FSR	1.6	2.1
Mean Time from Trial Start to FSIV	0.4	0.4
Mean Time from Trial Start to LSR	21	25.7
Mean # of Sites Opened	149	149
Mean # of Subjects Screened per Site	4.7	5.87
Mean # of Screen Failures	0	174.817
Mean # of Sites with at least 1 Subject Screened	139.333	129.409
Mean Randomization Rate/Site	0.423	0.302
Output Time Unit	Months	Months



Overall Trial Duration

Scenario 3

- Site failure ratio = 0.1 & Screen failure ratio = 0.2



Other Features

- Milestone Probability
- Compare Plans
- Interim Analysis
- Import Functionality
- Edit Plan
- User Friendly UI

Summary

- Major challenge - Planning
- Simulation - better prediction
- EnForeSys:
 - Uses Monte Carlo Simulations
 - Realistic forecasting technique
 - Accounts for non-linearity and randomness
- Reduces study costs and timelines
- Maximizes chances of study success.

References

- EnForeSys User Manual
- Impact Report Tufts CSDD, 2013
- *Li, Gen and Gray, Robert*, “ Performance-Based Site Selection Reduces Costs and Shortens Enrollment Time”, 2011
- *Hess, Jon*, “ Web-Based Patient Recruitment,” Cutting Edge information, <http://www.cuttingedgeinfo.com/process/?ref=122>

