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**Better planning through design:
Modeling and forecasting enrollment and event arrivals
to optimize trial execution**

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- Introduction
- Benefits of modeling and forecasting recruitment and event accruals
- A simulation study
- Case study: Phase 3 in oncology
- Concluding remarks

Some facts and figures

- According to a recent report in Cutting Edge Information, clinical trials last 42% longer than expected in Phase I, 31% longer in Phase II, and 30% beyond planned deadlines in Phase III - all because of recruitment delays. (Beasely, "Recruiting". 2008)
- Six percent of clinical trials are completed on time, and 72% of trials run over schedule by more than one month. (www.fda.gov)
- Eighty percent of total trials are delayed at least one month because of unfulfilled enrollment. (Lamberti, "State of Clinical Trials Industry", 292)

- Out of all of the research sites in the United States, less than 1/3 contain 70% of the valuable subjects. Therefore 70% of the research sites under-perform, and somewhere between 15%-20% never enroll a single patient. (Pierre, "Recruitment and Retention". 2006)
- Fifty percent of clinical research sites enroll one or no patients in their studies. (Pierre, "Recruitment and Retention". 2006)

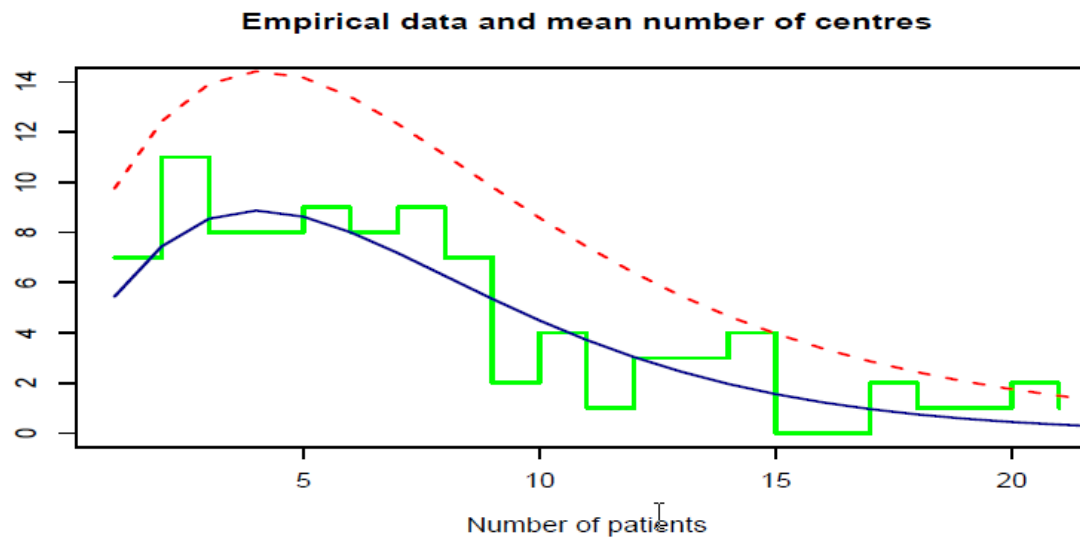
Benefits of modeling

Meeting patient recruitment challenges in clinical trials

Why model patient recruitment?

- Significant resources and strategic planning are contingent upon the timing of interim and final data analyses
- Modeling recruitment and event accrual based on current accumulated data allows early and accurate predictions of interim analysis times and study termination
- Statistical modeling also provides confidence levels for predictions

- Randomness is natural and accounts for many observed phenomena in recruitment (Anisimov, 2009)



- Randomness in recruitment coupled with randomization can substantially affect the statistical validity of study results; and have major implications on the very costly drug supply chain process

- Opening new centers to meet recruitment deadlines
- Optimizing (avoiding drug shortage or overage) drug supply chain to meet predicted demand based on recruitment, retention, and randomization forecasts
- Cost savings:
 - Can centers be closed?
 - Can drug supply be redirected to other sites?
 - Can site monitoring be better planned for CRAs to spend time where most needed?

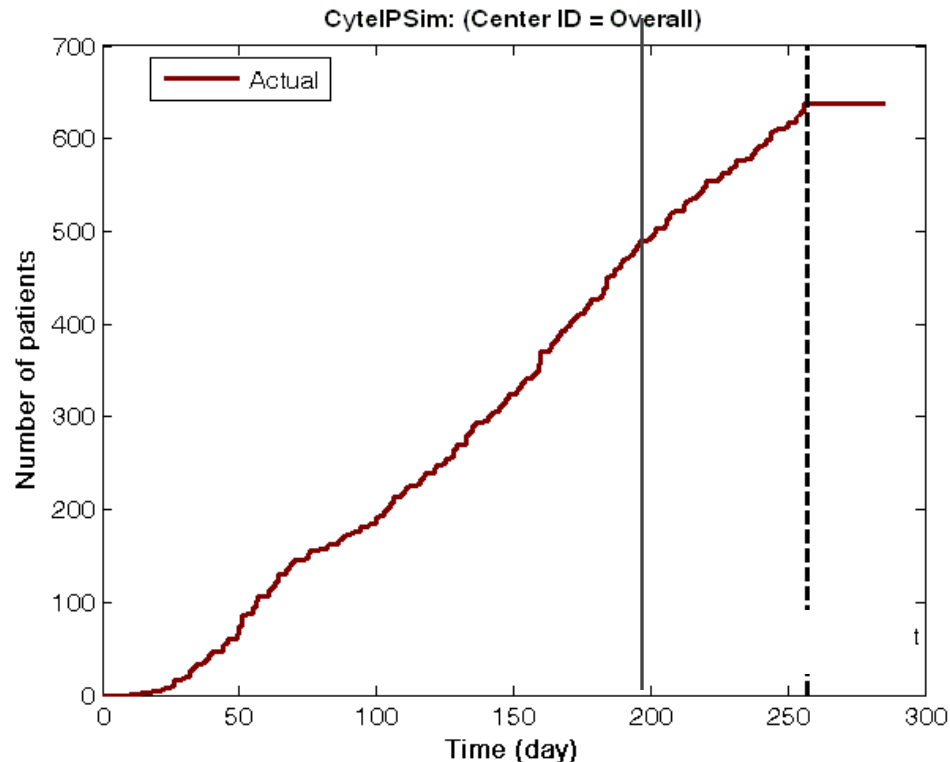
Simulation Study

How the simulation model works

- Number of subjects to be enrolled = 640
- Target recruitment period = 200 days
- 21 sites in US, estimated approximately equally spaced Site Initiation Visit (SIV) times between day 1 and day 50, av. time = 25 days
- Average enrollment rate per site to achieve target given estimated SIV times is about 3.5 patients/site/month (0.17 patients/site/day)
- Clinical Operations estimated Standard Deviation of enrollment rate between sites to be about 50% of the average (0.085 patients/day)

What really happened

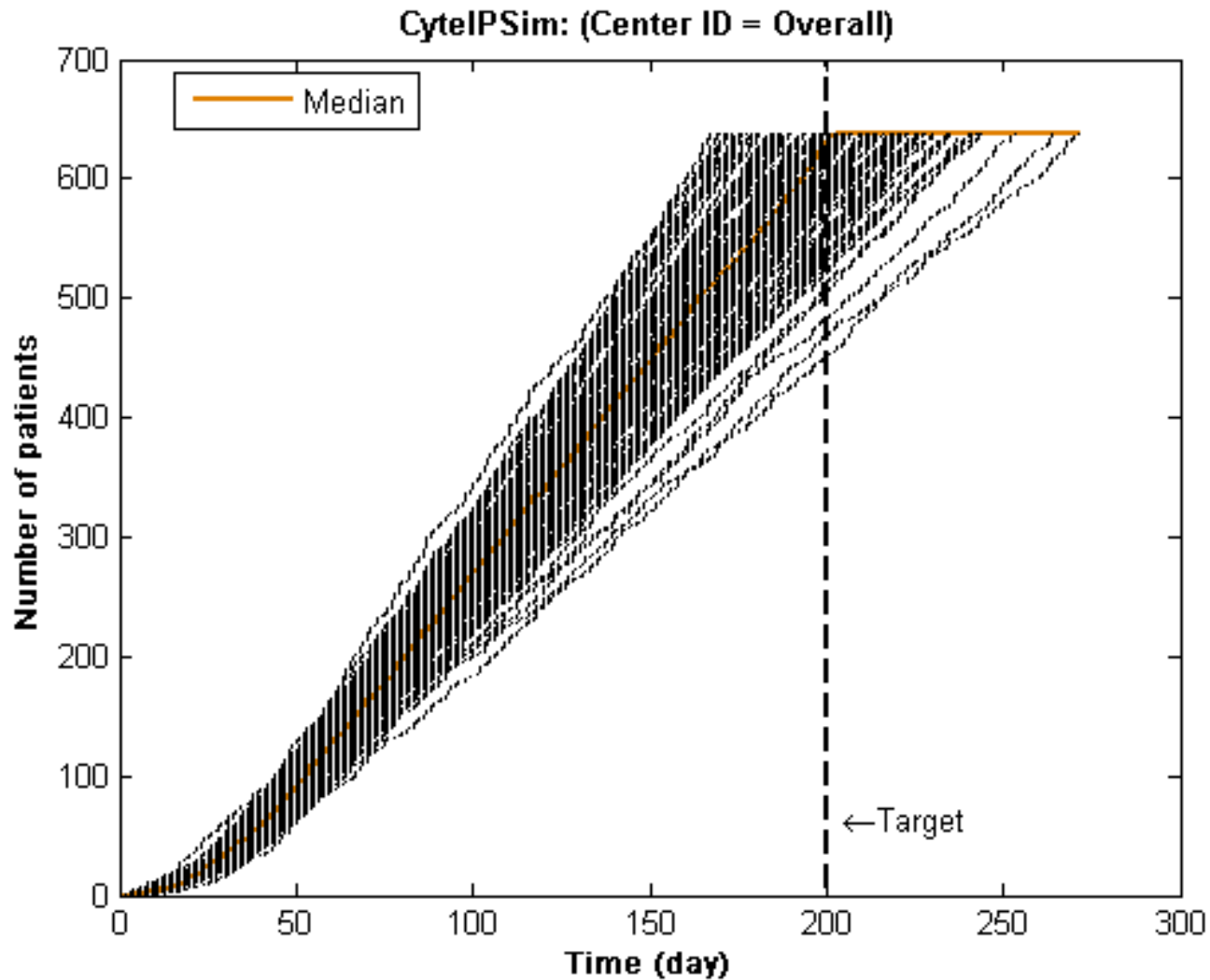
- Actually recruitment took 255 days
- Site opening took longer than anticipated: last site SIV was 143 days and average SIV time was about 60% longer than planned



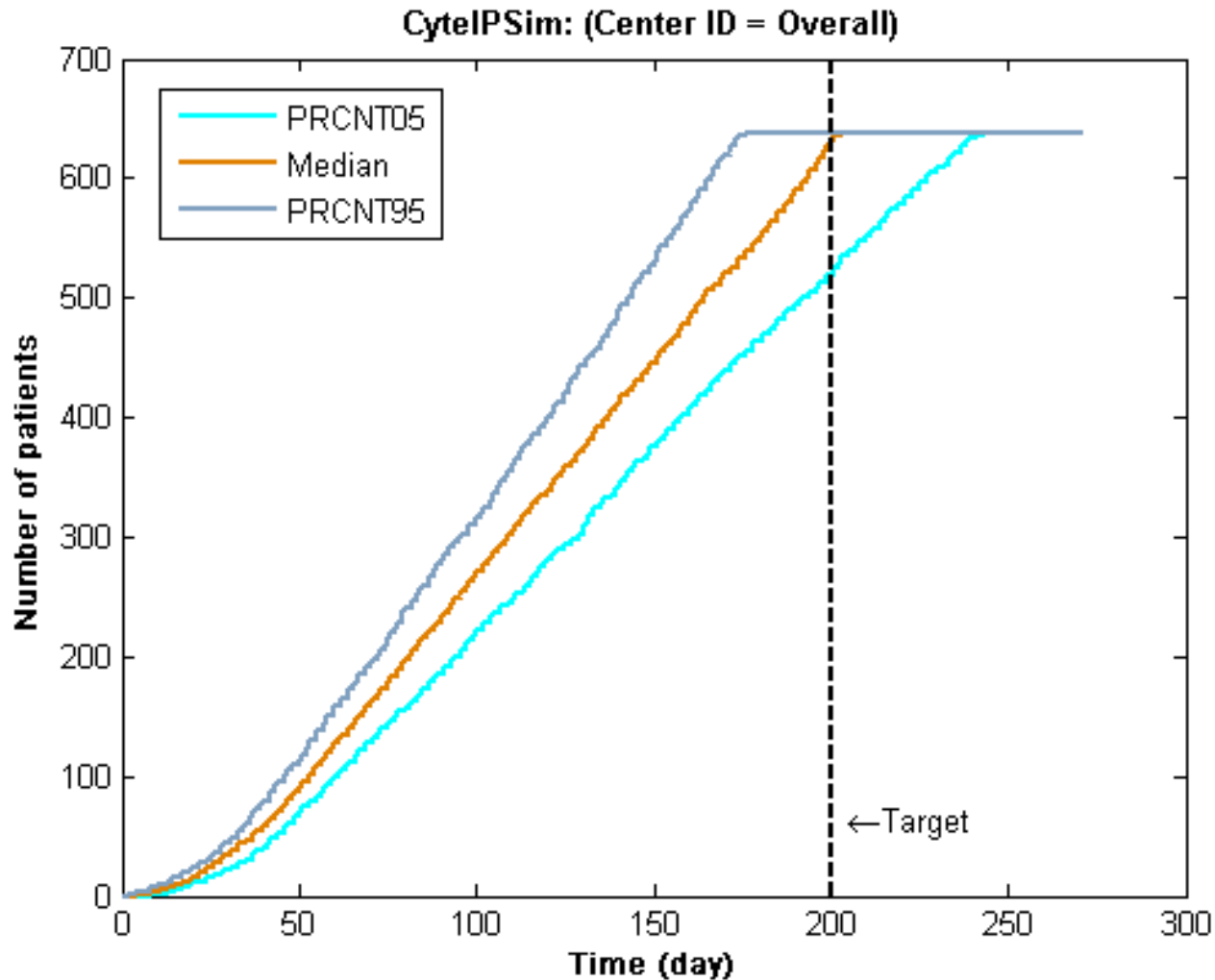
Estimated SIV times

| Site ID | Est. SIV | Actual SIV |
|---------|----------|------------|
| 1 | 45 | 140 |
| 2 | 5 | 7 |
| 3 | 45 | 133 |
| 4 | 10 | 8 |
| 5 | 15 | 13 |
| 6 | 25 | 20 |
| 7 | 25 | 16 |
| 8 | 50 | 143 |
| 9 | 30 | 21 |
| 10 | 10 | 8 |
| 11 | 40 | 130 |
| 12 | 40 | 55 |
| 13 | 1 | 2 |
| 14 | 1 | 1 |
| 15 | 15 | 8 |
| 16 | 20 | 13 |
| 17 | 35 | 29 |
| 18 | 5 | 4 |
| 19 | 20 | 15 |
| 20 | 35 | 29 |
| 21 | 30 | 28 |

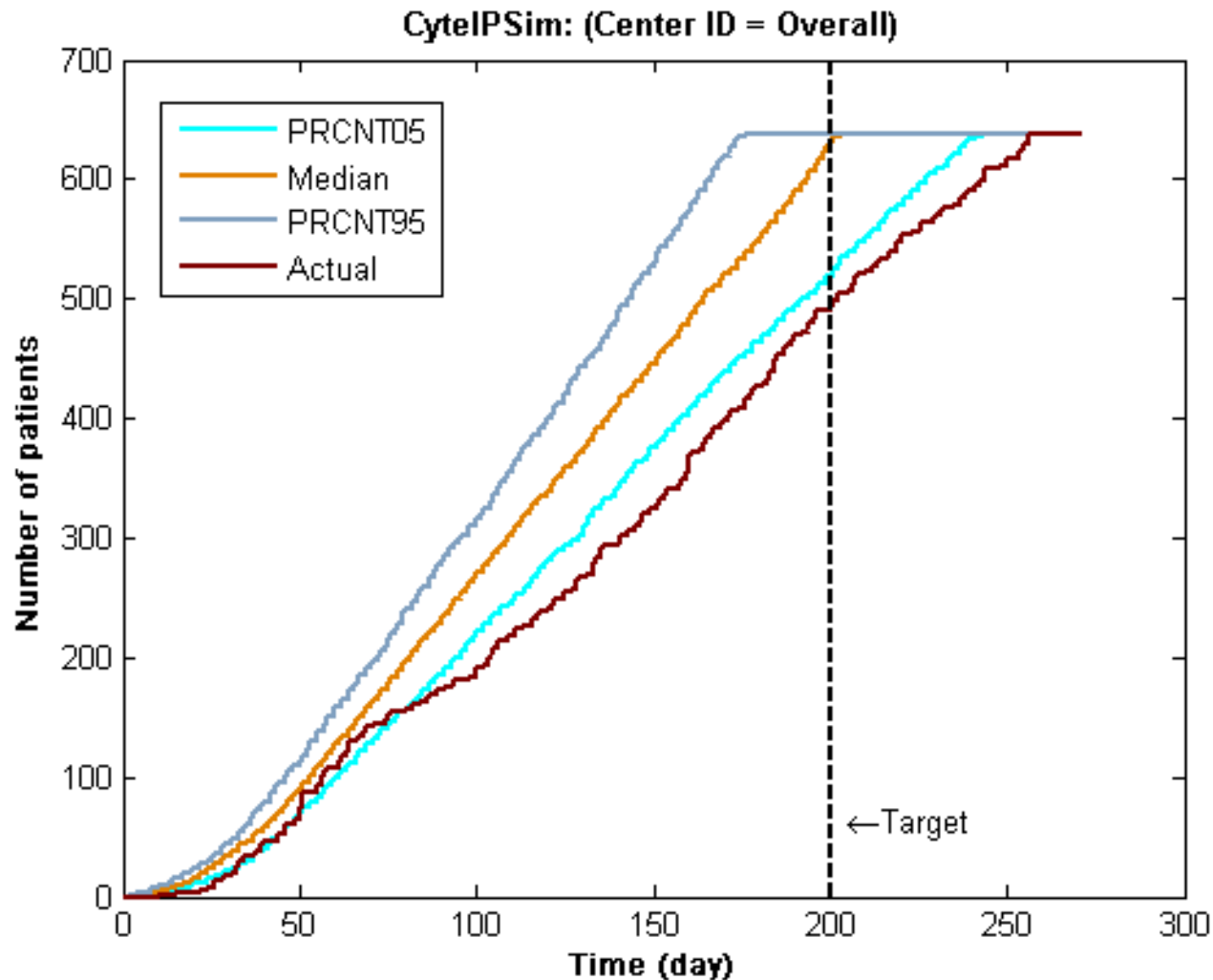
100 simulations at study design time



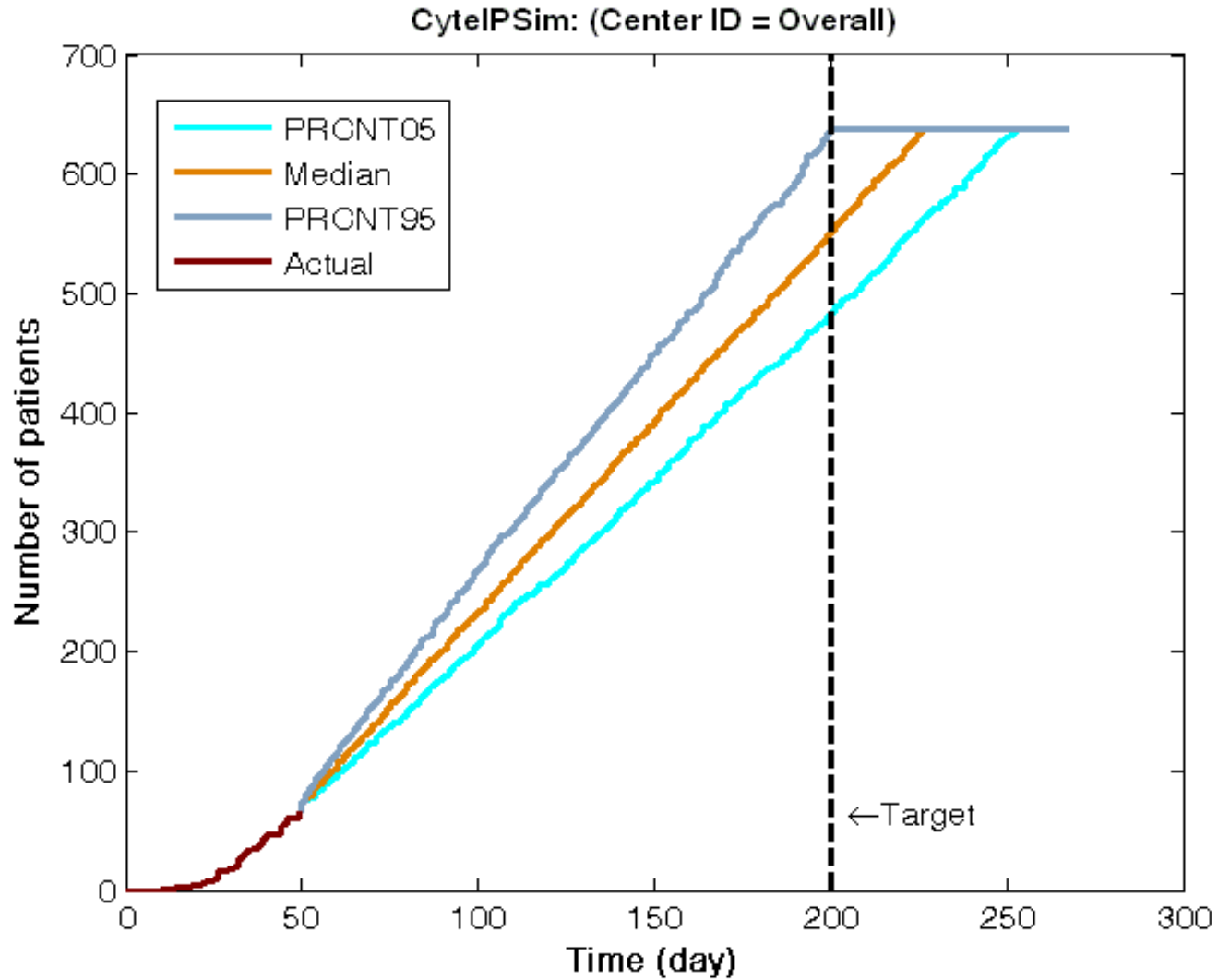
Study design time recruitment forecast



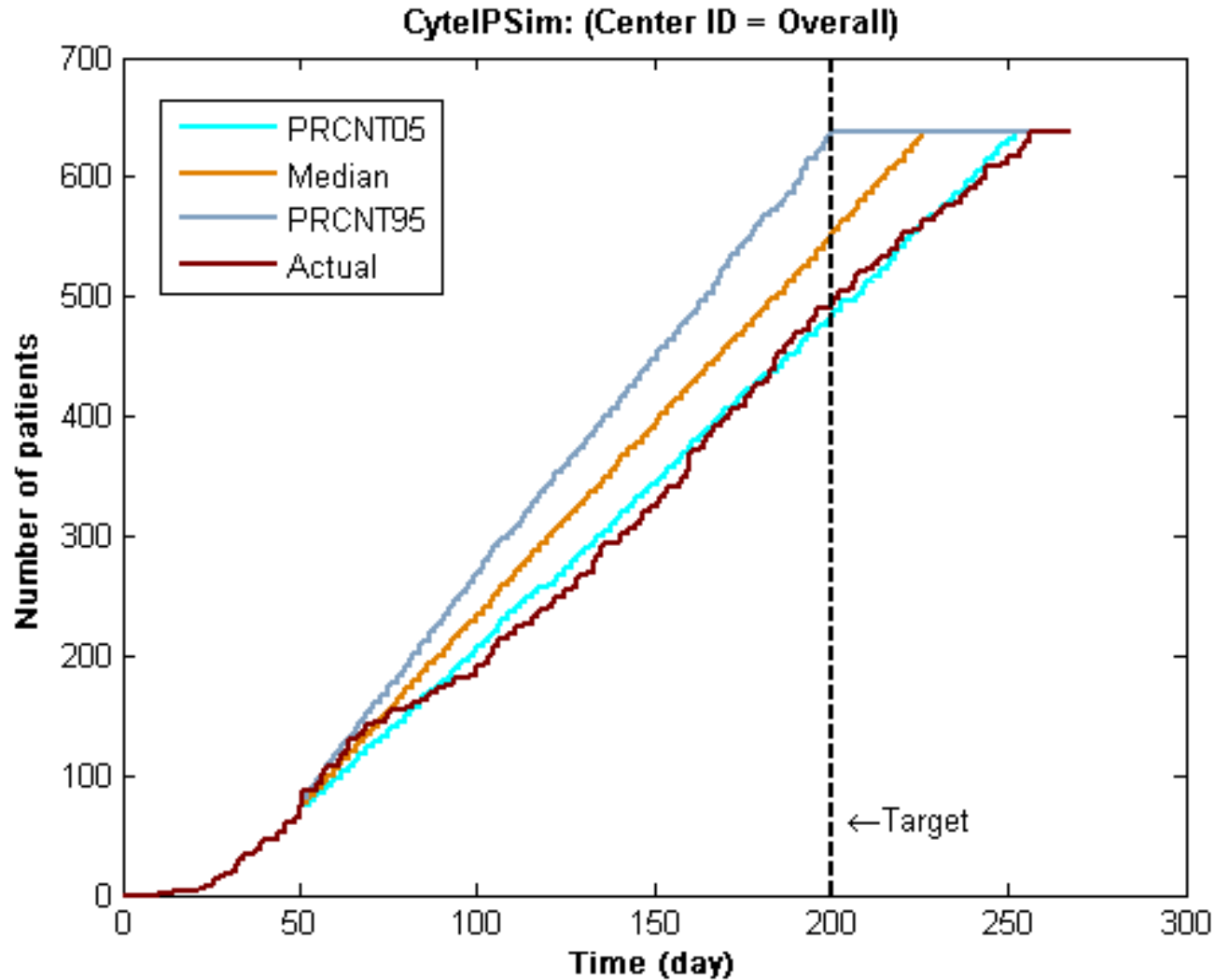
Study design time forecast and actual



Forecast after 50 days

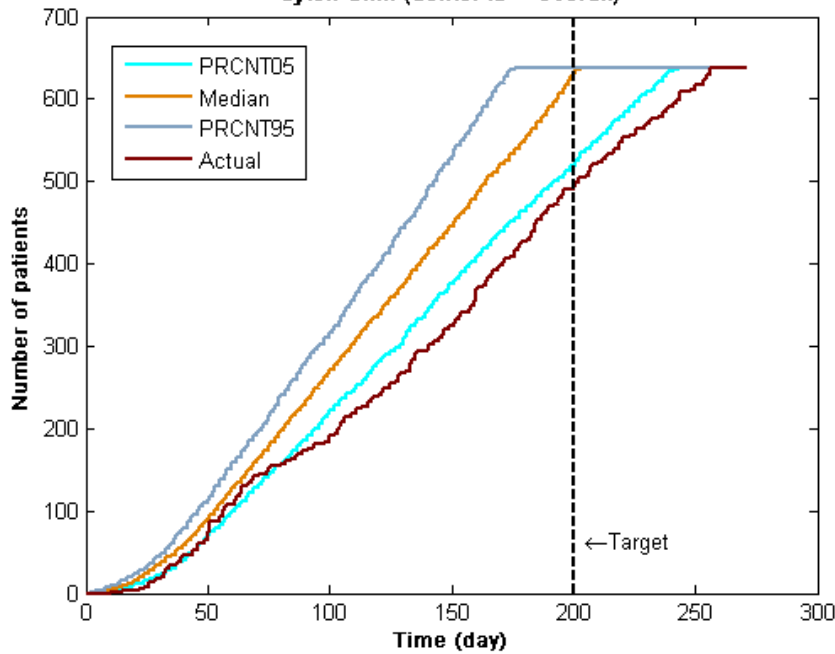


Forecast after 50 days with actual

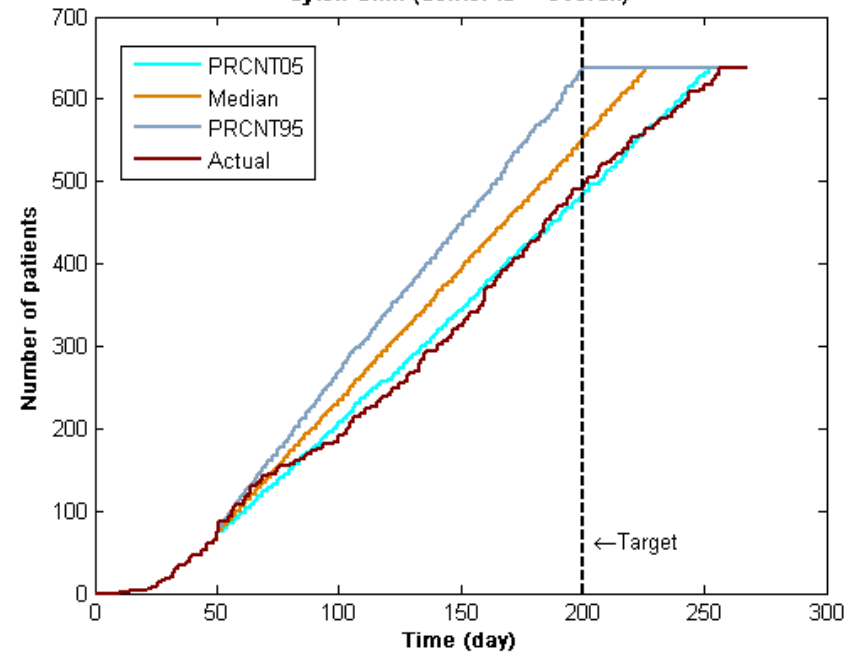


Forecasts after 0 and 50 days

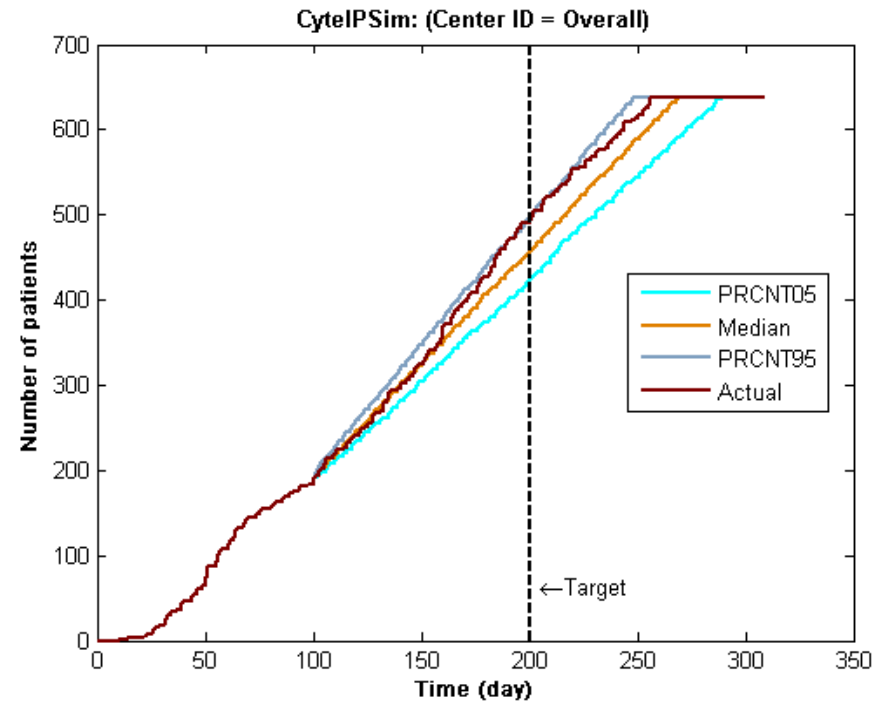
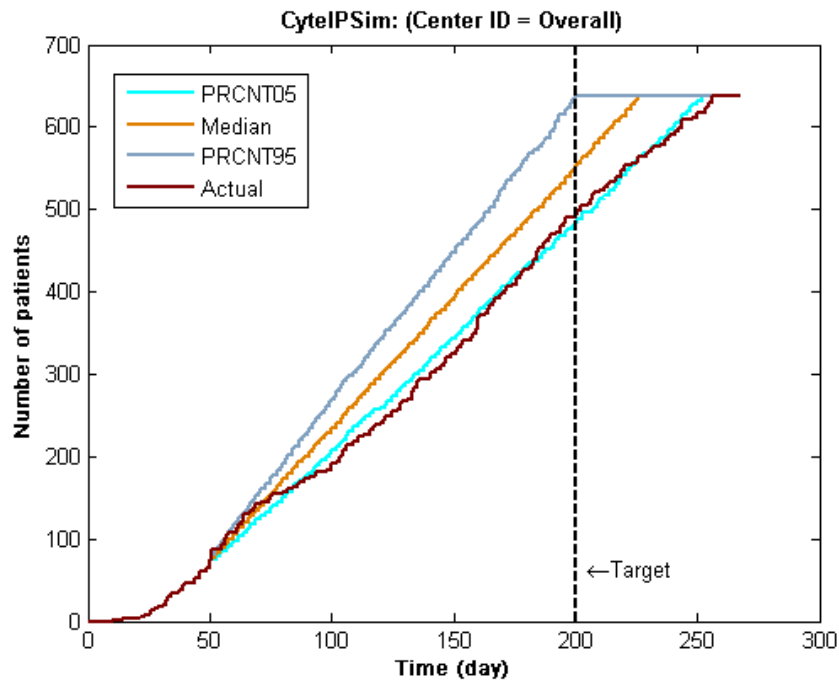
CytelPSim: (Center ID = Overall)



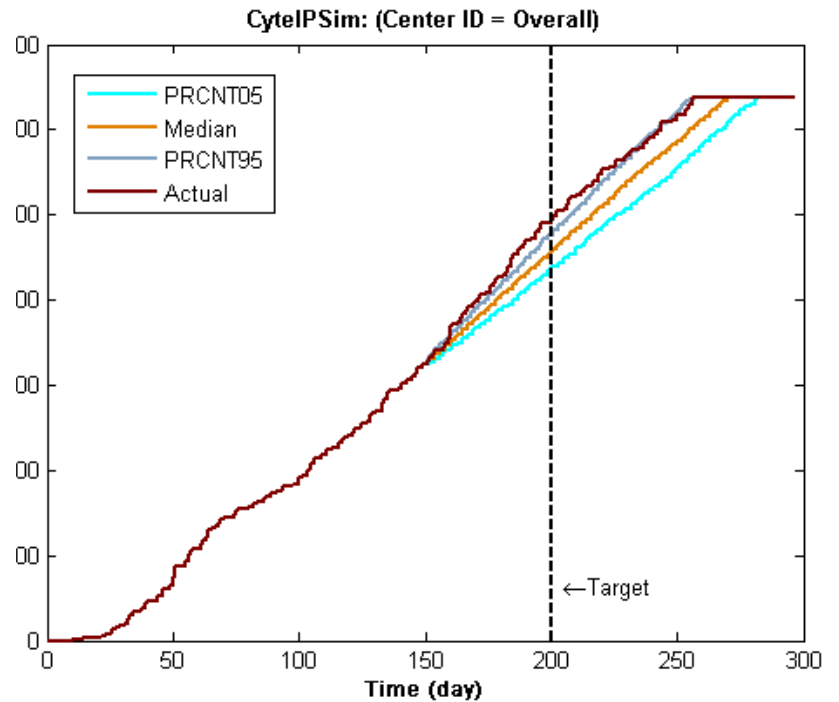
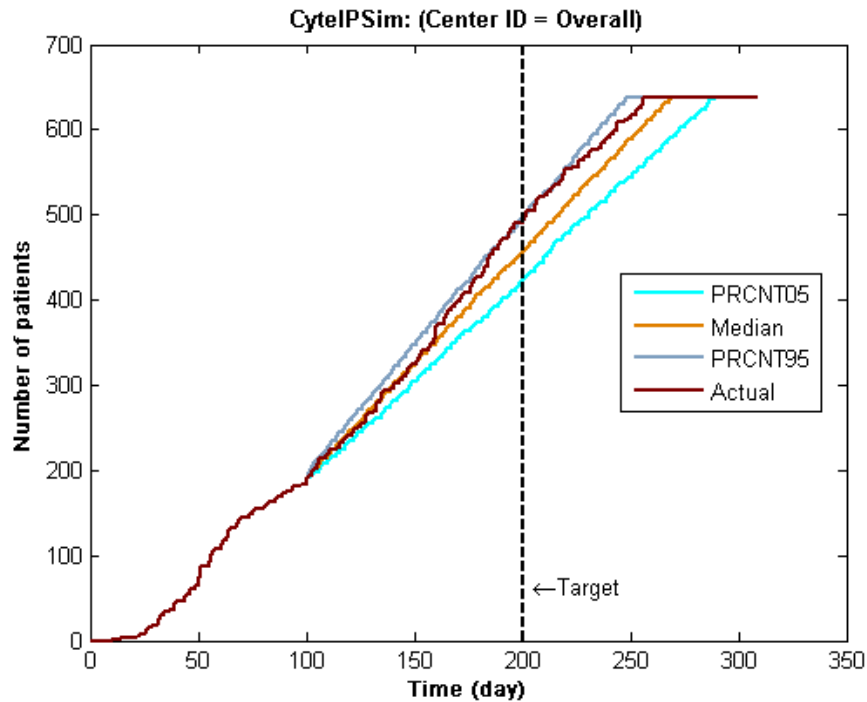
CytelPSim: (Center ID = Overall)



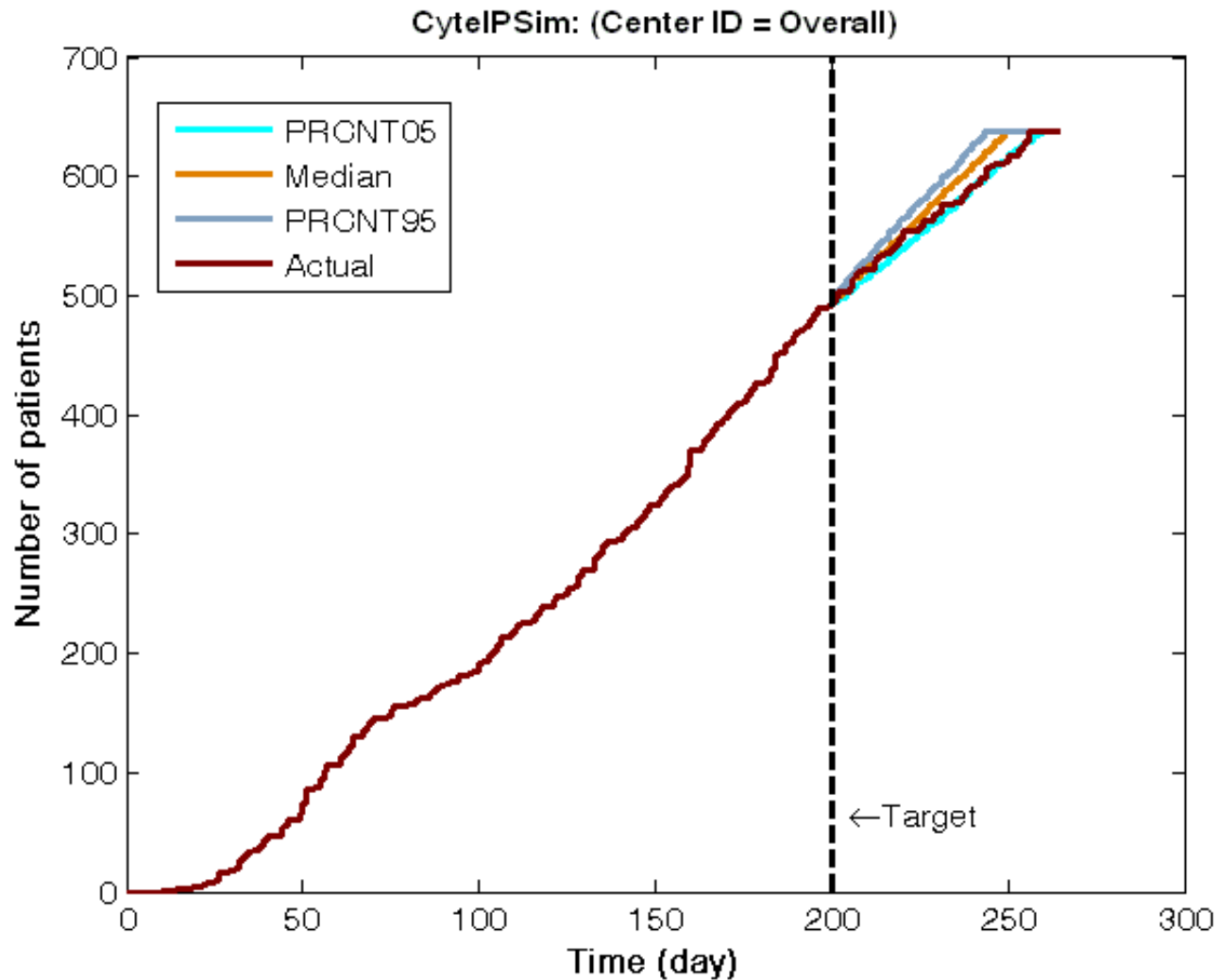
Forecasts after 50 and 100 days



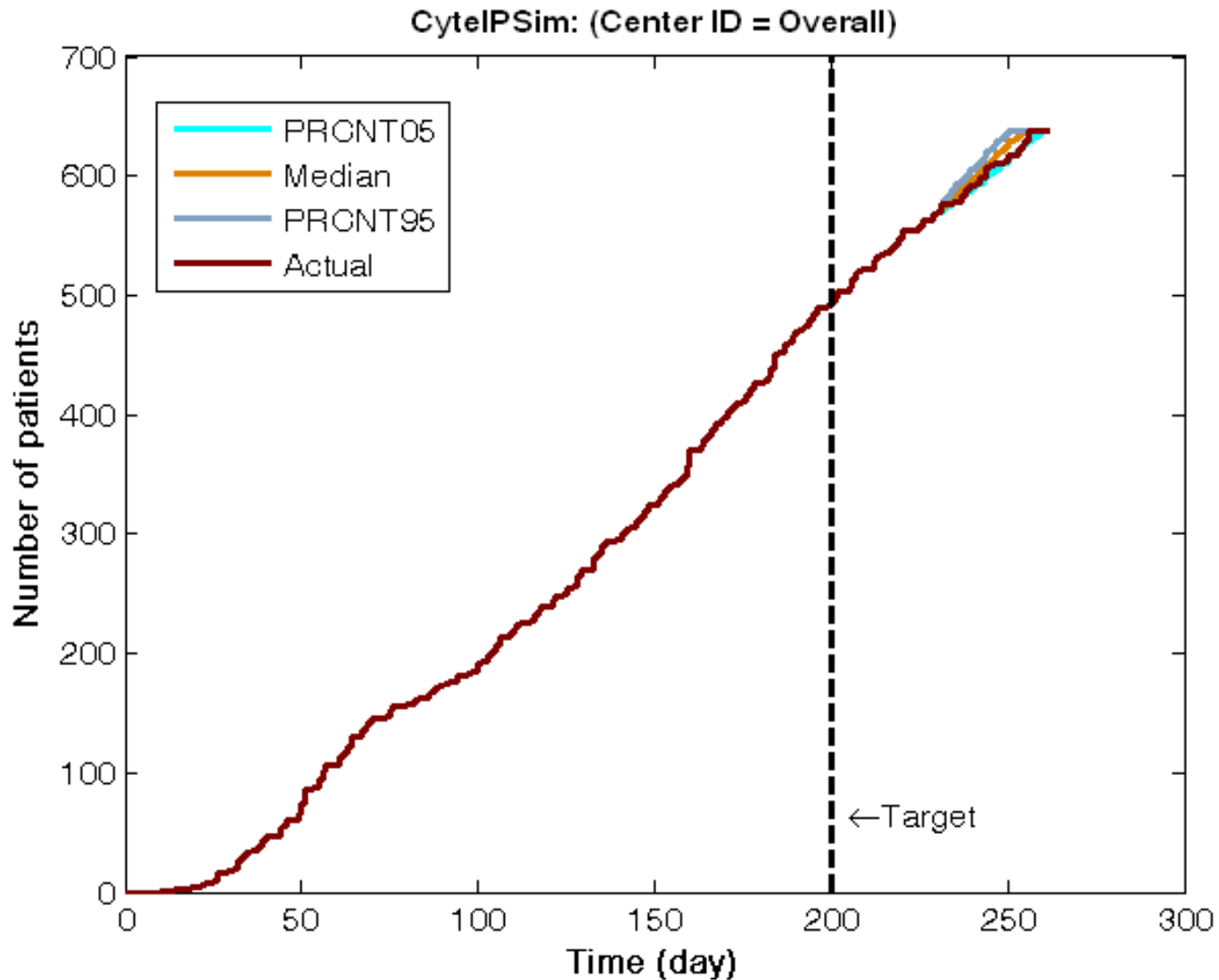
Forecasts after 100 and 150 days



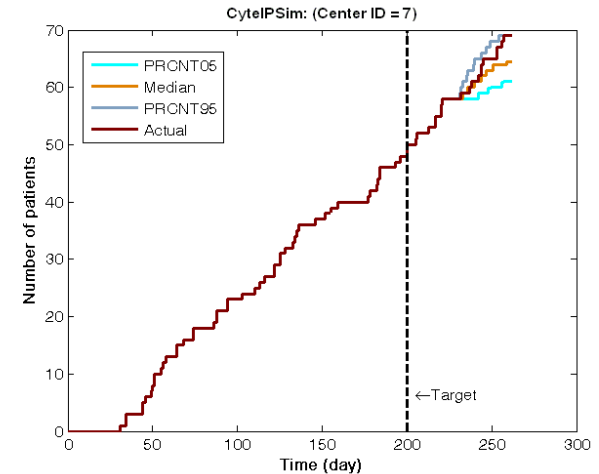
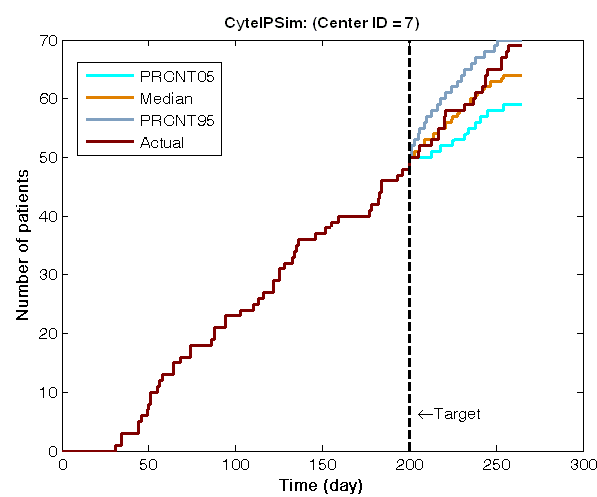
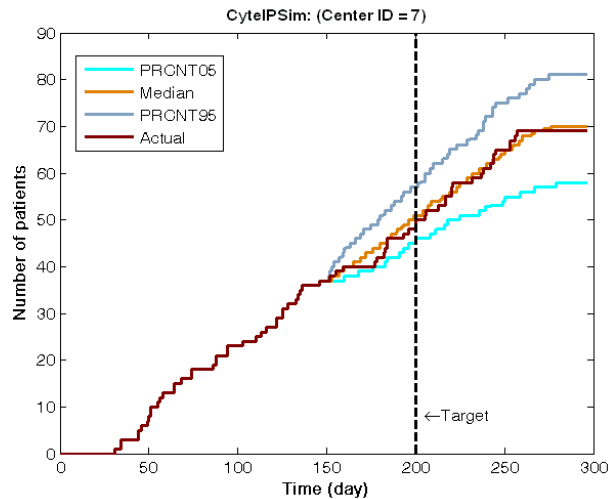
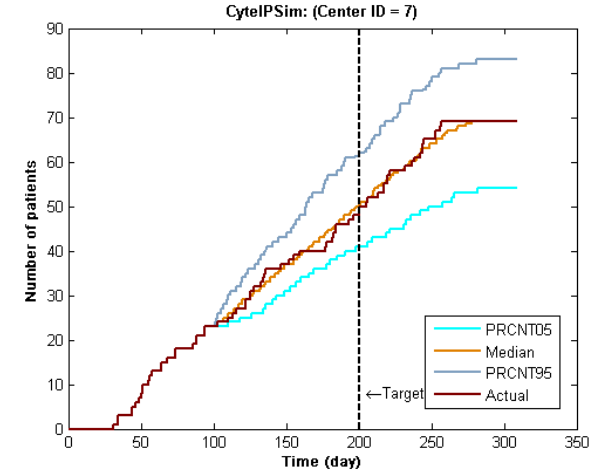
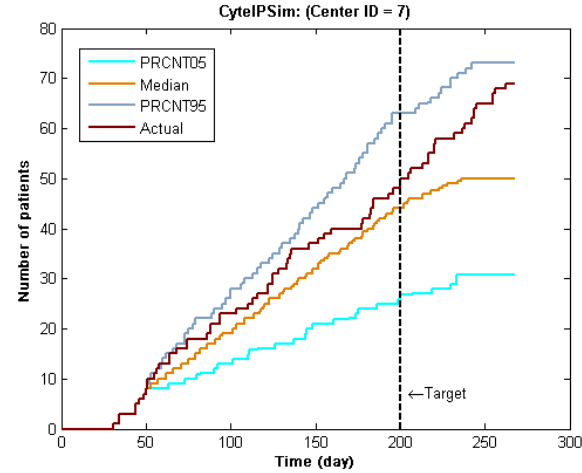
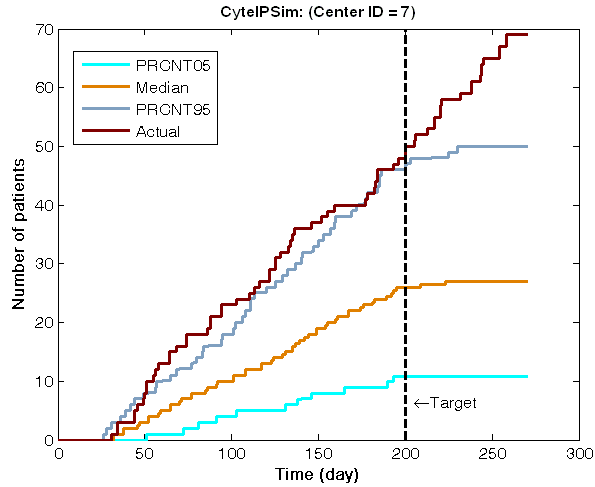
Forecast after 200 days with actual



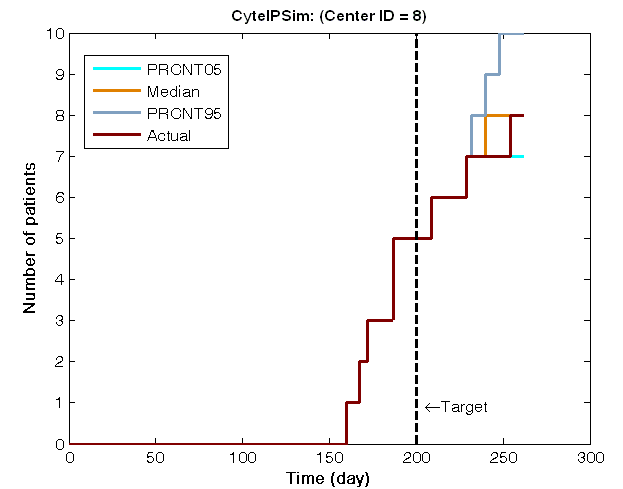
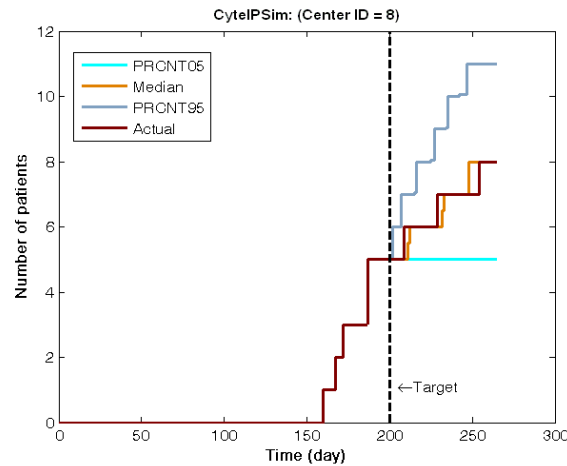
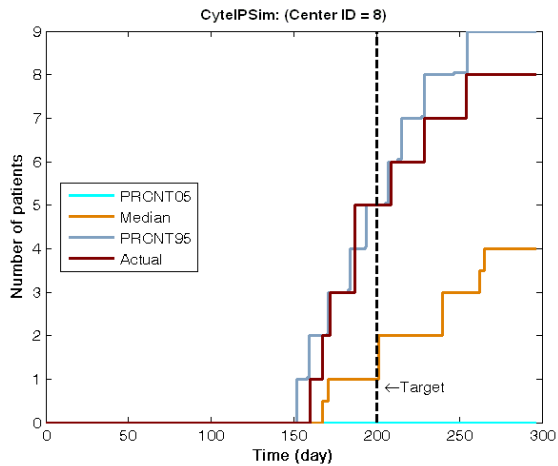
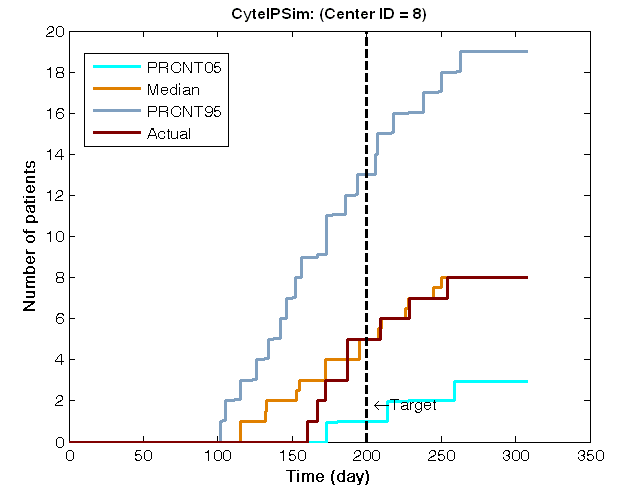
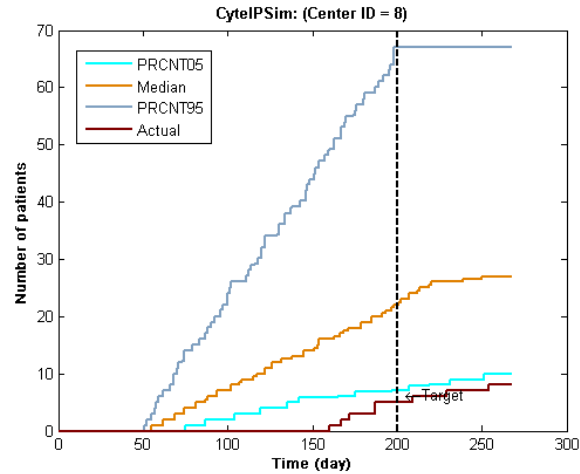
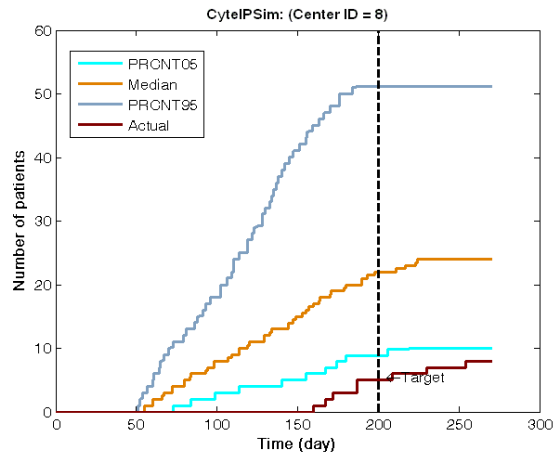
Forecast after 230 days with actual



Drilling down: Site 7 high recruiting (69 subj)



Drilling down: Site 8 low recruiting (8 subj)



Case Study

Phase 3 trial in patients with relapsed multiple myeloma

Probability of achieving milestones

In this study, Bayesian methods have been used to predict three variables (enrollment, events, dropouts) while targeting two sample sizes (500,750) under three different assumptions of enrollment scenarios (Low, Medium, High).

Enrollment Scenarios:

- a) **Low Enrollment Scenario** implies **1/2 of average enrollment rates*** used as priors for Poisson-Gamma model
- b) **Medium Enrollment Scenario** implies **3/4th of average enrollment rates*** used as priors for Poisson-Gamma model
- c) **High Enrollment Scenario** implies **average enrollment rates*** used as priors for Poisson-Gamma model

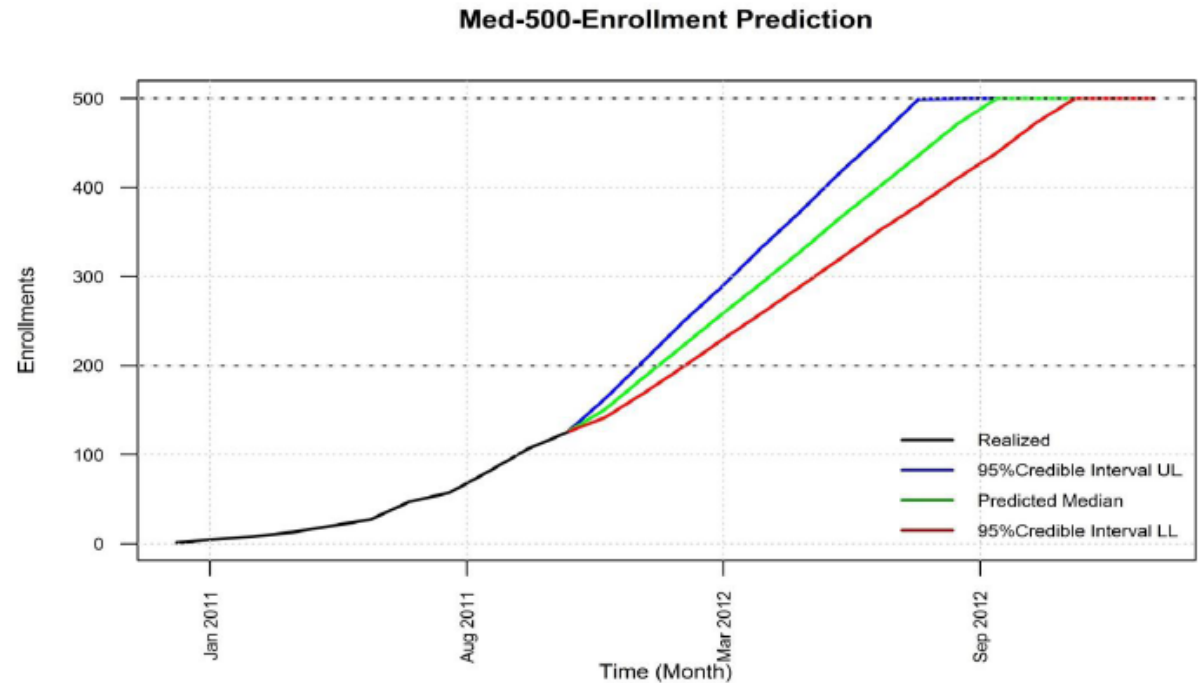
| No. | Milestone | Probability of Achieving Milestone*** | | |
|-----|--|---------------------------------------|----------------------------|--------------------------|
| | | Low Enrollment Scenario | Medium Enrollment Scenario | High Enrollment Scenario |
| 1 | 200 patients enrolled by 31 Dec 2011 | 0.001 | 0.088 | 0.402 |
| 2 | 500 patients enrolled by 31 Dec 2012 without increased sample size | 0.686 | 0.998 | 1 |
| 3 | 750 patients enrolled by 30 Sep 2013 with increased sample size | 0.582 | 0.997 | 1 |
| 4 | 187 Death events for Interim analysis by the DSMB by 31 Aug 2012 | 0.924 | 0.997 | 1 |
| 5 | 375 Death events for final analysis by the DSMB by 31 Aug 2013 without increased sample size | 0.878 | 0.935 | 0.951 |
| 6 | 562 Death events for final analysis by the DSMB by 31 May 2014 with increased sample size | 0.88 | 0.971 | 0.983 |

*** Probabilities are computed based on 1000 simulated trials. Probability of 1 indicates that the milestone was reached in all the 1000 simulated trials. Strictly speaking, it should be interpreted as 0.999+, as higher number of simulated trials may lead to one or more trials not meeting the milestone.

500 subject enrollment prediction

Enrollments-500

| Month End | Enrollments | | |
|-----------|-------------|--------|-------------|
| | 95%C.I.(LL) | Median | 95%C.I.(UL) |
| Dec-10 | 1 | 1 | 1 |
| Jan-11 | 5 | 5 | 5 |
| Feb-11 | 8 | 8 | 8 |
| Mar-11 | 13 | 13 | 13 |
| Apr-11 | 20 | 20 | 20 |
| May-11 | 27 | 27 | 27 |
| Jun-11 | 47 | 47 | 47 |
| Jul-11 | 57 | 57 | 57 |
| Aug-11 | 81 | 81 | 81 |
| Sep-11 | 106 | 106 | 106 |
| Oct-11 | 125 | 125 | 125 |
| Nov-11 | 142 | 151 | 163 |
| Dec-11 | 170 | 188 | 207 |
| Jan-12 | 200 | 224 | 251 |
| Feb-12 | 229 | 258 | 289 |
| Mar-12 | 259 | 293 | 333 |
| Apr-12 | 289 | 328 | 373 |
| May-12 | 320 | 366 | 417 |
| Jun-12 | 351 | 400 | 456 |
| Jul-12 | 380 | 436 | 499 |
| Aug-12 | 411 | 472 | 500 |
| Sep-12 | 439 | 500 | 500 |
| Oct-12 | 473 | 500 | 500 |
| Nov-12 | 500 | 500 | 500 |

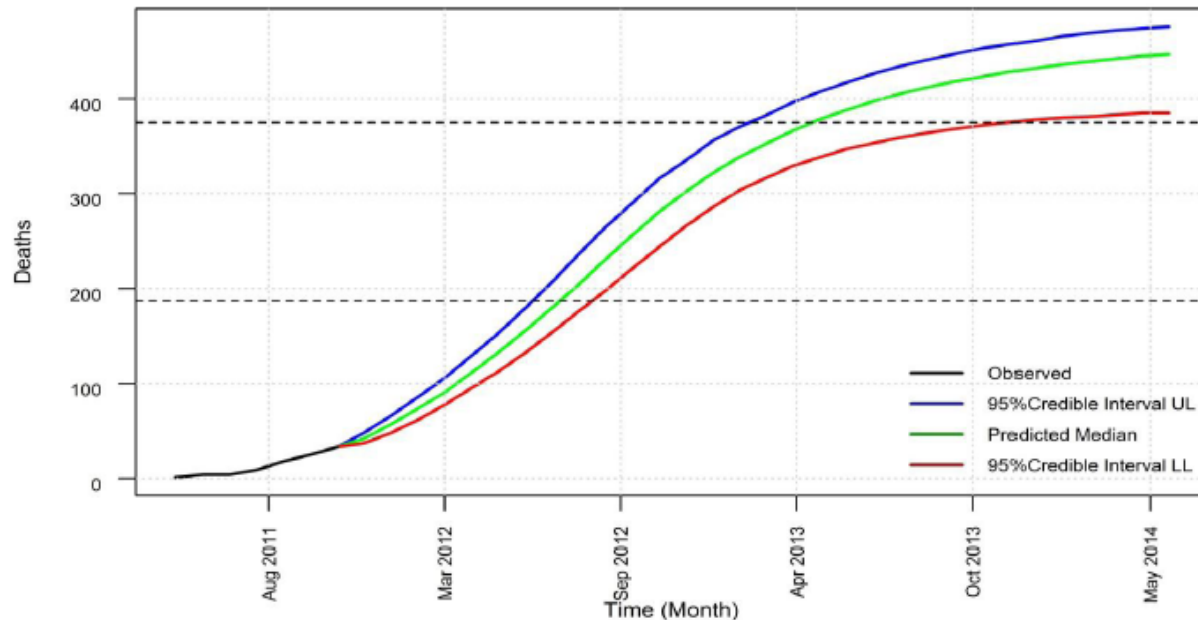


Event prediction to reach 187-375 targets

Death-Events-187-375

| Month End | Death Events | | |
|-----------|--------------|--------|-------------|
| | 95%C.I.(LL) | Median | 95%C.I.(UL) |
| Apr-11 | 1 | 1 | 1 |
| May-11 | 4 | 4 | 4 |
| Jun-11 | 4 | 4 | 4 |
| Jul-11 | 9 | 9 | 9 |
| Aug-11 | 18 | 18 | 18 |
| Sep-11 | 25 | 25 | 25 |
| Oct-11 | 33 | 33 | 33 |
| Nov-11 | 37 | 42 | 48 |
| Dec-11 | 48 | 57 | 66 |
| Jan-12 | 62 | 74 | 86 |
| Feb-12 | 77 | 90 | 105 |
| Mar-12 | 95 | 111 | 129 |
| Apr-12 | 112 | 132 | 152 |
| May-12 | 132 | 155 | 179 |
| Jun-12 | 153 | 179 | 206 |
| Jul-12 | 176 | 204 | 236 |
| Aug-12 | 198 | 231 | 265 |
| Sep-12 | 221 | 256 | 290 |
| Oct-12 | 244 | 281 | 316 |
| Nov-12 | 266 | 302 | 335 |
| Dec-12 | 286 | 322 | 356 |
| Jan-13 | 304 | 339 | 371 |
| Feb-13 | 316 | 352 | 382 |
| Mar-13 | 329 | 366 | 396 |
| Apr-13 | 338 | 378 | 407 |
| May-13 | 347 | 388 | 417 |
| Jun-13 | 353 | 397 | 426 |
| Jul-13 | 359 | 405 | 434 |
| Aug-13 | 364 | 412 | 441 |
| Sep-13 | 368 | 418 | 447 |
| Oct-13 | 372 | 423 | 453 |
| Nov-13 | 375 | 428 | 457 |

Med-500-Death Events Prediction

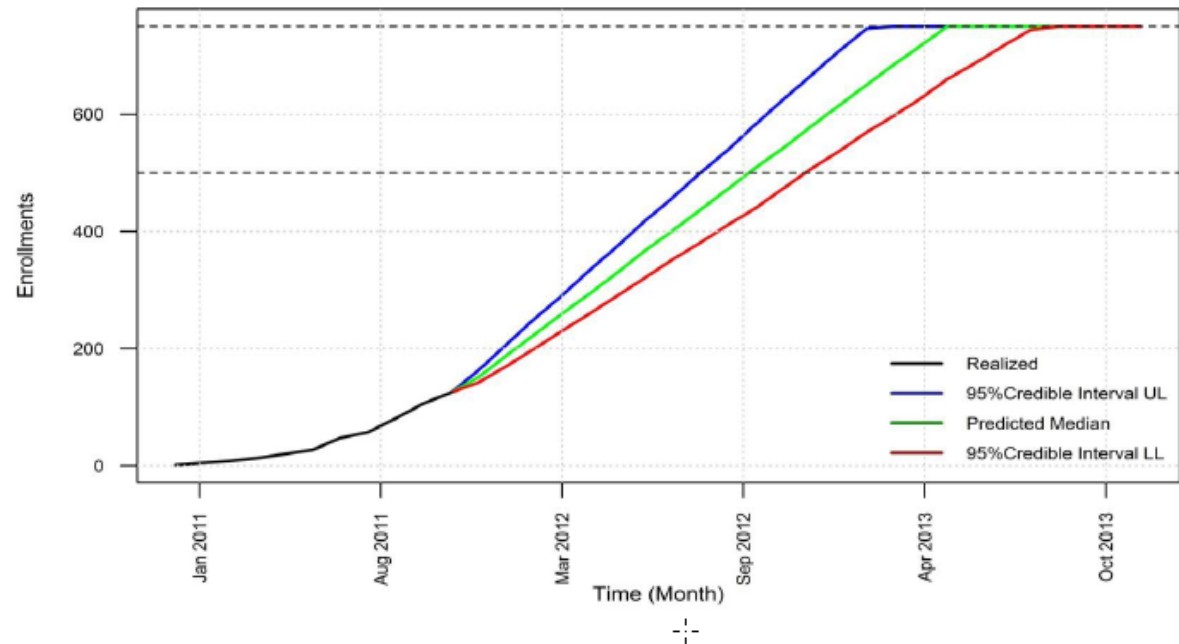


Enrollment prediction to reach 750 subj

Enrollments-750

| Month End | Enrollments | | |
|-----------|-------------|--------|-------------|
| | 95%C.I.(LL) | Median | 95%C.I.(UL) |
| Dec-10 | 1 | 1 | 1 |
| Jan-11 | 5 | 5 | 5 |
| Feb-11 | 8 | 8 | 8 |
| Mar-11 | 13 | 13 | 13 |
| Apr-11 | 20 | 20 | 20 |
| May-11 | 27 | 27 | 27 |
| Jun-11 | 47 | 47 | 47 |
| Jul-11 | 57 | 57 | 57 |
| Aug-11 | 81 | 81 | 81 |
| Sep-11 | 106 | 106 | 106 |
| Oct-11 | 125 | 125 | 125 |
| Nov-11 | 142 | 151 | 163 |
| Dec-11 | 170 | 188 | 207 |
| Jan-12 | 200 | 224 | 251 |
| Feb-12 | 229 | 258 | 289 |
| Mar-12 | 259 | 293 | 333 |
| Apr-12 | 289 | 328 | 373 |
| May-12 | 320 | 366 | 417 |
| Jun-12 | 351 | 400 | 456 |
| Jul-12 | 380 | 436 | 499 |
| Aug-12 | 411 | 472 | 539 |
| Sep-12 | 439 | 508 | 582 |
| Oct-12 | 473 | 542 | 625 |
| Nov-12 | 506 | 578 | 665 |
| Dec-12 | 536 | 614 | 707 |
| Jan-13 | 569 | 650 | 746 |
| Feb-13 | 595 | 682 | 750 |
| Mar-13 | 626 | 716 | 750 |
| Apr-13 | 660 | 750 | 750 |
| May-13 | 687 | 750 | 750 |
| Jun-13 | 716 | 750 | 750 |
| Jul-13 | 744 | 750 | 750 |
| Aug-13 | 750 | 750 | 750 |

Med-750-Enrollment Prediction

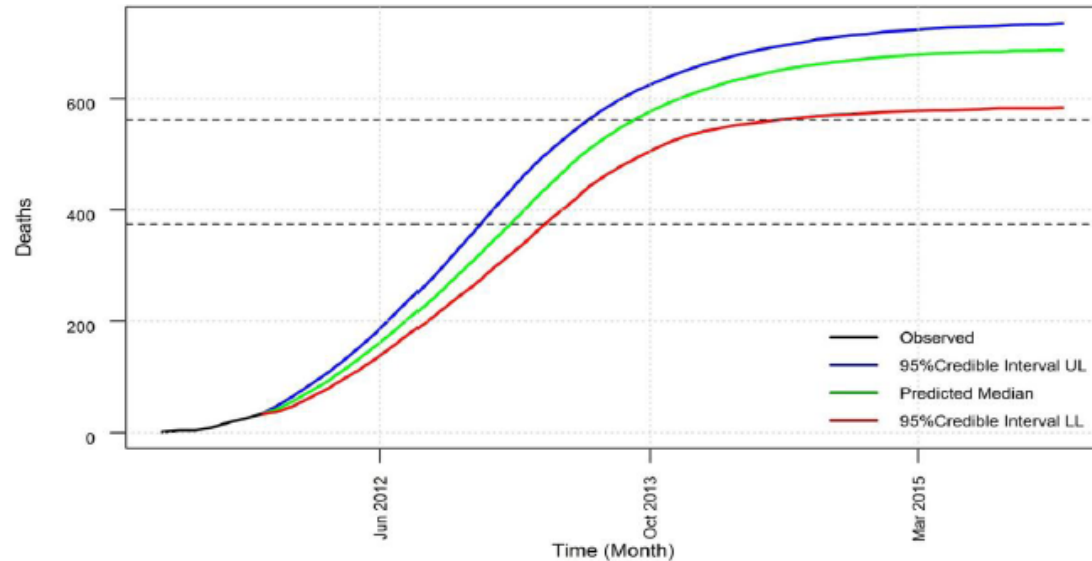


Event prediction to reach 562 target

Death-Events-562

| Month End | Death Events | | |
|--------------|--------------|--------|-------------|
| | 95%C.I.(LL) | Median | 95%C.I.(UL) |
| Apr-11 | 1 | 1 | 1 |
| May-11 | 4 | 4 | 4 |
| Jun-11 | 4 | 4 | 4 |
| Jul-11 | 9 | 9 | 9 |
| Aug-11 | 18 | 18 | 18 |
| Sep-11 | 25 | 25 | 25 |
| Oct-11 | 33 | 33 | 33 |
| Nov-11 | 37 | 42 | 48 |
| Dec-11 | 48 | 57 | 66 |
| Jan-12 | 63 | 74 | 86 |
| Feb-12 | 77 | 90 | 105 |
| Mar-12 | 95 | 111 | 128 |
| Apr-12 | 112 | 132 | 152 |
| May-12 | 132 | 155 | 178 |
| Jun-12 | 153 | 178 | 207 |
| Jul-12 | 176 | 204 | 237 |
| Aug-12 | 198 | 230 | 266 |
| Sep-12 | 221 | 256 | 297 |
| Oct-12 | 245 | 285 | 331 |
| Nov-12 | 266 | 312 | 363 |
| Dec-12 | 293 | 342 | 398 |
| Jan-13 | 317 | 371 | 431 |
| Feb-13 | 339 | 398 | 461 |
| Mar-13 | 367 | 429 | 491 |
| Apr-13 | 392 | 456 | 516 |
| May-13 | 415 | 485 | 541 |
| Jun-13 | 442 | 509 | 563 |
| Jul-13 | 462 | 530 | 583 |
| Aug-13 | 480 | 550 | 601 |
| Sep-13 | 495 | 566 | 616 |
| Oct-13 | 510 | 581 | 629 |
| Nov-13 | 523 | 594 | 641 |
| Dec-13 | 534 | 606 | 652 |
| Jan-14 | 542 | 616 | 662 |
| Feb-14 | 547 | 625 | 670 |
| Mar-14 | 553 | 634 | 678 |
| Apr-14 | 556 | 640 | 685 |
| May-14 | 560 | 647 | 691 |

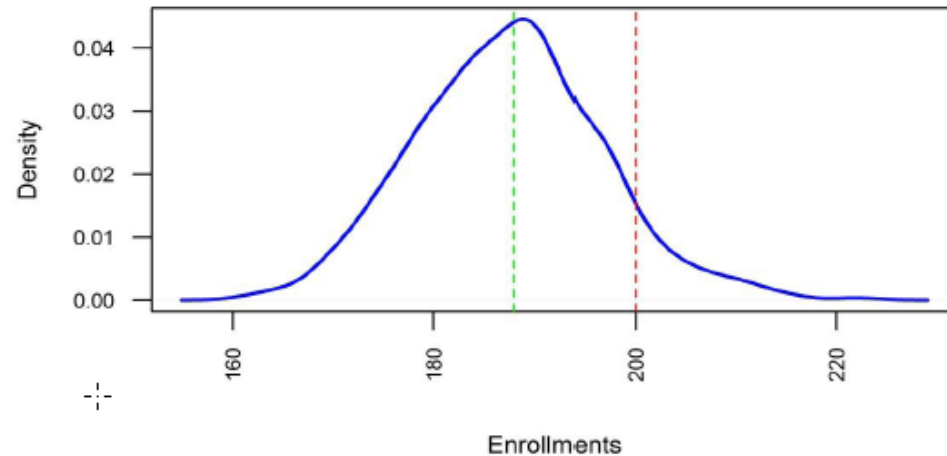
Med-750-Death Events Prediction



Milestones probability distribution

| Event | Milestone | Prediction Date | Probability |
|---|-----------|-----------------|-------------|
| Enrolment Milestones | | | |
| First Year Enrolments | 200 | 31-12-11 | 0.088 |
| | | 31-01-12 | 0.978 |
| Enrolments without Increased Sample Size | 500 | 31-07-12 | 0.025 |
| | | 31-08-12 | 0.202 |
| | | 30-09-12 | 0.582 |
| | | 31-10-12 | 0.889 |
| | | 30-11-12 | 0.98 |
| | | 31-12-12 | 0.998 |
| Enrolments with Increased Sample Size | 750 | 31-12-12 | 0.002 |
| | | 31-01-13 | 0.022 |
| | | 28-02-13 | 0.097 |
| | | 31-03-13 | 0.257 |
| | | 30-04-13 | 0.504 |
| | | 31-05-13 | 0.755 |
| | | 30-06-13 | 0.909 |
| | | 31-07-13 | 0.968 |
| | | 31-08-13 | 0.991 |
| | | 30-09-13 | 0.997 |

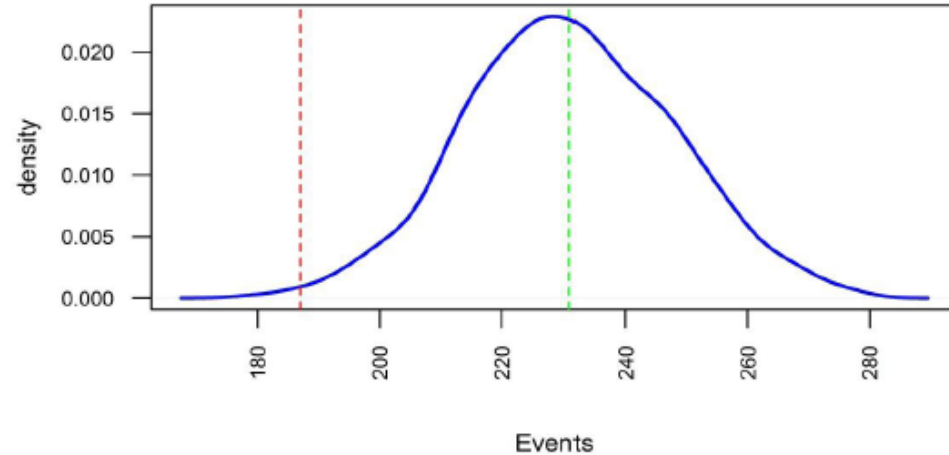
Enrollment Probability Distribution as on 12/31/11



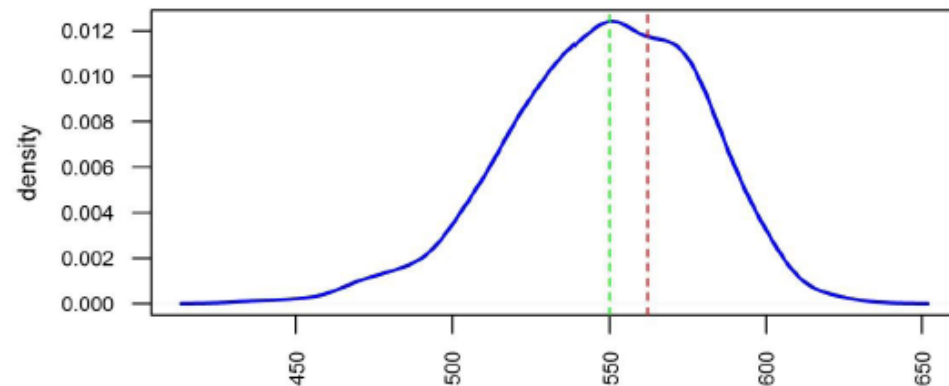
Event milestones probability distribution

| Event | Milestone | Prediction Date | Probability |
|---|-----------|-----------------|-------------|
| Death Events Milestones | | | |
| Death Events for Interim Analysis | 187 | 31-05-12 | 0.009 |
| | | 30-06-12 | 0.284 |
| | | 31-07-12 | 0.9 |
| | | 31-08-12 | 0.997 |
| Death Events for Final Analysis without Increased Sample Size | 375 | 31-01-13 | 0.017 |
| | | 28-02-13 | 0.074 |
| | | 31-03-13 | 0.306 |
| | | 30-04-13 | 0.577 |
| | | 31-05-13 | 0.758 |
| | | 30-06-13 | 0.849 |
| | | 31-07-13 | 0.912 |
| | | 31-08-13 | 0.935 |
| Death Events for Final Analysis with Increased Sample Size | 562 | 31-05-13 | 0.004 |
| | | 30-06-13 | 0.028 |
| | | 31-07-13 | 0.15 |
| | | 31-08-13 | 0.364 |
| | | 30-09-13 | 0.567 |
| | | 31-10-13 | 0.74 |
| | | 30-11-13 | 0.851 |
| | | 31-12-13 | 0.903 |
| | | 31-01-14 | 0.935 |
| | | 28-02-14 | 0.952 |
| | | 31-03-14 | 0.961 |
| | | 30-04-14 | 0.965 |
| | | 31-05-14 | 0.971 |

Death Events Probability Distribution as on 08/31/12



Death Events Probability Distribution as on 08/31/13



Monitoring site performance

| Site Performance | | | | | | | | | |
|------------------|---------|-----------------|----------------------|----------------------------|----------------------------|-----------------|-------------------|----------------------------|----------------------------|
| Country | Site Id | Activation Date | Enrolment rate/Month | Realized as on 07 Nov 2011 | Expected as on 07 Nov 2011 | Performance Gap | % Performance Gap | Prediction for 31 Dec 2011 | Prediction for 31 Aug 2012 |
| Australia | 601 | 23-07-11 | 0.16 | 2 | 0.5 | 1.5 | 264% | 2.5 | 5.0 |
| Australia | 602 | 29-04-11 | 0.56 | 0 | 3.6 | (3.6) | (100%) | 0.2 | 1.2 |
| Australia | 603 | 15-08-11 | 0.94 | 1 | 2.6 | (1.6) | (61%) | 1.9 | 6.1 |
| Australia | 604 | 08-04-11 | 0.19 | 0 | 1.3 | (1.3) | (100%) | 0.1 | 0.8 |
| Australia | 605 | 11-05-11 | 0.16 | 1 | 0.9 | 0.1 | 8% | 1.3 | 2.6 |
| Australia | 606 | 20-06-11 | 0.75 | 0 | 3.5 | (3.5) | (100%) | 0.3 | 1.7 |
| Australia | 607 | 04-08-11 | 0.22 | 2 | 0.7 | 1.3 | 192% | 2.7 | 5.8 |
| Australia | 608 | 04-10-11 | 0.19 | 0 | 0.2 | (0.2) | (100%) | 0.3 | 1.5 |
| Australia | 609 | | 0.25 | 0 | | | | 0.4 | 2.4 |
| Australia | 610 | 23-08-11 | 0.34 | 1 | 0.9 | 0.1 | 16% | 1.7 | 4.6 |
| Australia | 611 | 23-07-11 | 0.19 | 0 | 0.7 | (0.7) | (100%) | 0.2 | 1.1 |
| Austria | 401 | | 0.22 | 0 | | | | 0.4 | 2.1 |
| Austria | 402 | | 0.75 | 0 | | | | 1.3 | 7.4 |
| Austria | 403 | 30-08-11 | 0.47 | 0 | 1.1 | (1.1) | (100%) | 0.4 | 2.2 |
| Austria | 404 | 01-08-11 | 0.34 | 0 | 1.1 | (1.1) | (100%) | 0.3 | 1.6 |
| Belgium | 301 | 20-06-11 | 0.38 | 4 | 1.7 | 2.3 | 132% | 5.2 | 10.7 |
| Belgium | 302 | 11-07-11 | 0.19 | 0 | 0.7 | (0.7) | (100%) | 0.2 | 1.1 |
| Belgium | 303 | 29-06-11 | 0.75 | 4 | 3.2 | 0.8 | 24% | 5.6 | 12.7 |
| Belgium | 304 | 11-07-11 | 0.25 | 0 | 1.0 | (1.0) | (100%) | 0.2 | 1.2 |
| Belgium | 305 | 01-08-11 | 0.44 | 5 | 1.4 | 3.6 | 255% | 6.9 | 15.7 |
| Belgium | 306 | 11-07-11 | 0.19 | 0 | 0.7 | (0.7) | (100%) | 0.2 | 1.1 |
| Canada | 201 | 27-04-11 | 0.16 | 0 | 1.0 | (1.0) | (100%) | 0.1 | 0.8 |

Monitoring site performance

| Site Performance | | | | | | | | | |
|------------------|---------|-----------------|----------------------|----------------------------|----------------------------|-----------------|-------------------|----------------------------|----------------------------|
| Country | Site Id | Activation Date | Enrolment rate/Month | Realized as on 07 Nov 2011 | Expected as on 07 Nov 2011 | Performance Gap | % Performance Gap | Prediction for 31 Dec 2011 | Prediction for 31 Aug 2012 |
| Canada | 202 | 02-06-11 | 0.13 | 0 | 0.7 | (0.7) | (100%) | 0.1 | 0.7 |
| Canada | 203 | 16-06-11 | 0.38 | 0 | 1.8 | (1.8) | (100%) | 0.2 | 1.3 |
| Canada | 204 | 29-06-11 | 0.38 | 1 | 1.6 | (0.6) | (38%) | 1.5 | 3.8 |
| Canada | 205 | 20-07-11 | 0.31 | 0 | 1.1 | (1.1) | (100%) | 0.3 | 1.4 |
| CZ | 501 | 28-06-11 | 0.28 | 0 | 1.2 | (1.2) | (100%) | 0.2 | 1.2 |
| CZ | 502 | | 0.28 | 0 | | | | 0.5 | 2.8 |
| CZ | 503 | 14-10-11 | 0.28 | 0 | 0.2 | (0.2) | (100%) | 0.4 | 2.3 |
| France | 320 | 24-08-11 | 1.88 | 0 | 4.6 | (4.6) | (100%) | 0.6 | 3.3 |
| France | 321 | 12-10-11 | 0.75 | 0 | 0.6 | (0.6) | (100%) | 0.8 | 4.5 |
| France | 322 | 31-08-11 | 0.25 | 0 | 0.6 | (0.6) | (100%) | 0.3 | 1.6 |
| France | 323 | 03-10-11 | 0.16 | 0 | 0.2 | (0.2) | (100%) | 0.2 | 1.3 |
| France | 324 | 03-10-11 | 0.16 | 0 | 0.2 | (0.2) | (100%) | 0.2 | 1.3 |
| France | 325 | | 0.56 | 0 | | | | 1.0 | 5.5 |
| France | 326 | 03-10-11 | 0.38 | 0 | 0.4 | (0.4) | (100%) | 0.5 | 2.6 |
| France | 327 | 22-08-11 | 0.25 | 1 | 0.6 | 0.4 | 58% | 1.5 | 4.0 |
| France | 328 | | 0.28 | 0 | | | | 0.5 | 2.8 |
| Germany | 421 | 19-08-11 | 0.75 | 0 | 2.0 | (2.0) | (100%) | 0.4 | 2.5 |
| Germany | 422 | 02-09-11 | 0.75 | 3 | 1.6 | 1.4 | 84% | 5.0 | 14.2 |
| Germany | 423 | | 0.22 | 0 | | | | 0.4 | 2.1 |
| Germany | 424 | 06-09-11 | 1.13 | 0 | 2.3 | (2.3) | (100%) | 0.6 | 3.3 |
| Germany | 425 | 03-10-11 | 0.22 | 0 | 0.3 | (0.3) | (100%) | 0.3 | 1.7 |
| Germany | 426 | 05-09-11 | 0.14 | 0 | 0.3 | (0.3) | (100%) | 0.2 | 1.1 |

Monitoring country performance

| Country Performance | | | | | |
|---------------------|----------------------------|----------------------------|-----------------|----------------------------|----------------------------|
| Country | Realized as on 07 Nov 2011 | Expected as on 07 Nov 2011 | Performance Gap | Prediction for 31 Dec 2011 | Prediction for 31 Aug 2012 |
| Australia | 7 | 14.8 | (7.8) | 11.7 | 32.8 |
| Austria | 0 | 2.2 | (2.2) | 2.4 | 13.3 |
| Belgium | 13 | 8.8 | 4.2 | 18.3 | 42.5 |
| Canada | 1 | 6.2 | (5.2) | 2.3 | 8.1 |
| CZ | 0 | 1.4 | (1.4) | 1.1 | 6.3 |
| France | 1 | 7.2 | (6.2) | 5.7 | 26.7 |
| Germany | 7 | 7.0 | 0.0 | 14.1 | 46.4 |
| Hungary | 3 | 1.6 | 1.4 | 4.7 | 12.3 |
| ITALY | 7 | 6.5 | 0.5 | 10.8 | 28.1 |
| NewZealand | 1 | 4.6 | (3.6) | 2.2 | 7.6 |
| Poland | 1 | 3.3 | (2.3) | 4.3 | 19.0 |
| Spain | 2 | 5.8 | (3.8) | 3.8 | 11.8 |
| UK | 0 | 3.2 | (3.2) | 2.9 | 16.3 |
| US | 84 | 64.5 | 19.5 | 106.1 | 205.8 |
| Grand Total | 127 | 137 | (10.0) | 190 | 477 |

Concluding remarks

- Adaptive designs rely on being able to make decisions early enough (before end of recruitment) to change important aspects of the study design, for example:
 - sample size
 - early stopping / dropping treatment arms
 - randomization / treatment allocation ratios
 - patient inclusion/exclusion criteria
- Usually require rapidly observed endpoints and slow recruitment rates
- If recruitment needs to be slowed, then the trade-off between the benefits of adapting and those of rapid enrollment need to be investigated and assessed

- Modeling, simulating and forecasting enrollment and the arrival of events can help a sponsor or CRO get a grip on the uncertainty inherent in trial timelines
- This quantitative exercise combines with the “art of patient recruitment and retention” to run more efficient and successful studies
- Helps track issues such as poor-performing countries or sites, and guide decisions such as when to open new sites, or how and when to resupply sites with drug
- Cost savings can be substantial if impact on NPV, drug supply chain, and site monitoring is taken into account and acted upon

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