Simulation for Decision Making:

MSToolkit for Go/No Go

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Agenda

- Clinical Trial Simulation
- Using MSToolkit
- Informing Decisions

Clinical Trial Simulation
Why M&S?

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"I have always considered it more desirable to kill computer-generated patients than real ones while calibrating design parameters"

Peter Thall, MD Anderson Cancer Centre, Houston, TX

Clinical Trial Simulation
Why M&S?

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- Efficacy failures are making R&D expensive (51% Phase 2, 66% Phase 3)*
  - Differentiation against existing therapies
  - Benefit/risk & cost effectiveness
- Integrate understanding of human biology through modelling

* Current Position and Expectation for use of M&S in Drug Development and Regulatory Decision Making. Peter A Milligan. Parallel 2c, PSI 2012

Clinical Trial Simulation
How to Approach M&S?

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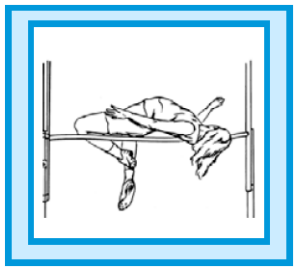
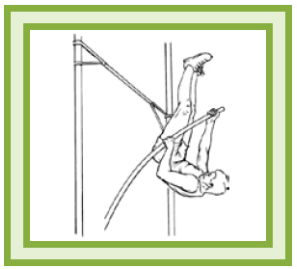
- MHRA support for M&S
- Regulators keen to see M&S being used
- Impact on submission based on usage

- Describe

- Justify



- Replace



Role of Modelling and Simulation in Regulatory Decision Making in Europe.
Terry Shepard. Parallel 2c, PSI 2012

Clinical Trial Simulation
How to Approach M&S?

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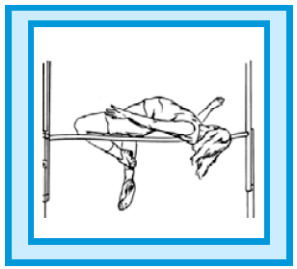
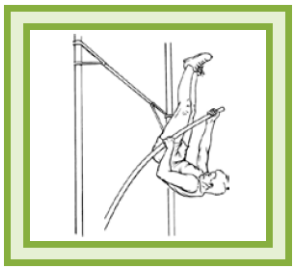
- Low Impact: Internal decision making, verify conclusions from preclinical FTIH

- Medium Impact: Dose ranging, justify not doing a study (e.g. PBPK)



- High Impact: Extrapolating efficacy/safety in new population



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Clinical Trial Simulation
How to Approach M&S?

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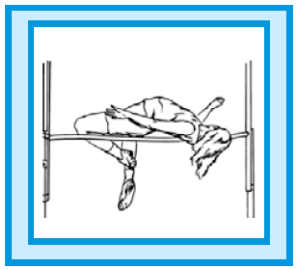
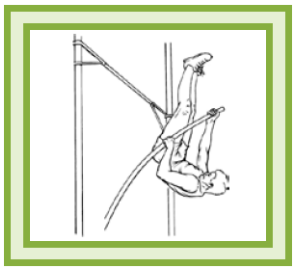
- M&S Good Practice





Role of Modelling and Simulation in Regulatory Decision Making in Europe.
Terry Shepard. Parallel 2c, PSI 2012

M&S Good Practice Target Decision

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- Know decision(s) that will be affected
- Benefits occur when decision is acted upon

Seven theses about good modelling: some reflections on modelling and simulation in the pharmaceutical industry. Stig Johan Wiklund & Carl-Fredrik Burman. Poster, PSI 2012

M&S Good Practice
Apply Scientific Knowledge

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- Diverse approaches may be necessary to solve problem efficiently, not statistics alone

Apply Scientific Knowledge

Target Decision

Seven theses about good modelling: some reflections on modelling and simulation in the pharmaceutical industry. Stig Johan Wiklund & Carl-Fredrik Burman. Poster, PSI 2012

M&S Good Practice Understand Question

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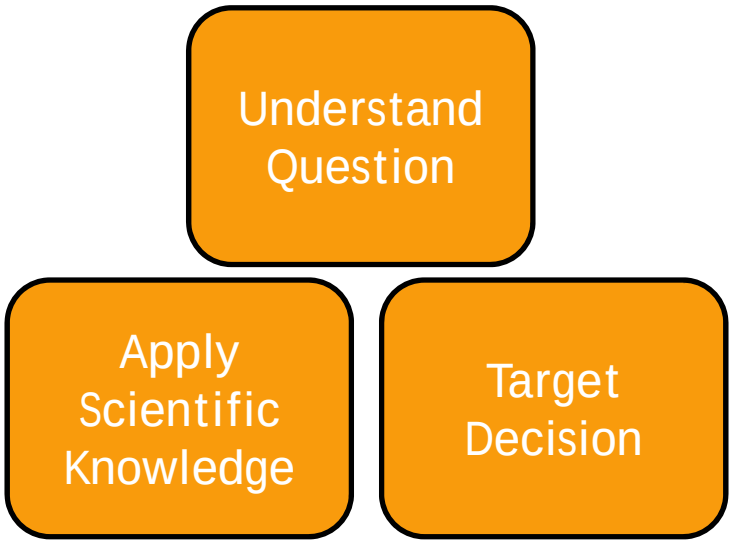
- "All models are wrong, but some are useful" *George Box*
- Incorporate information that is relevant to the decision



Seven theses about good modelling: some reflections on modelling and simulation in the pharmaceutical industry. Stig Johan Wiklund & Carl-Fredrik Burman. Poster, PSI 2012

M&S Good Practice
Keep it Simple

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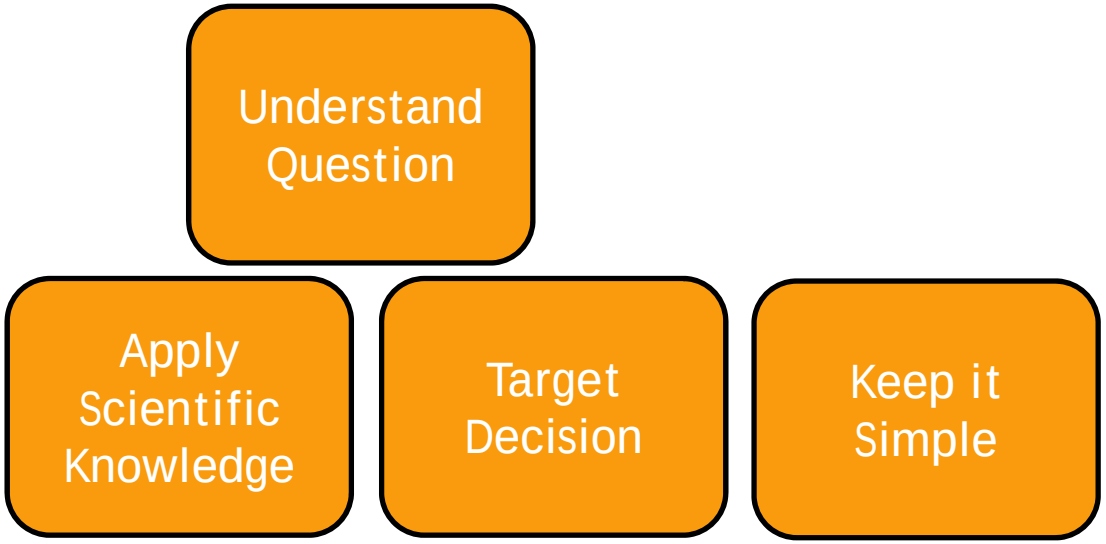

- "Pluralitas non est ponenda sine necessitate"
  John Duns Scotus
- Do not waste effort on features that do not affect decision
- Can parts of model be replaced with analytic or numeric solutions

Seven theses about good modelling: some reflections on modelling and simulation in the pharmaceutical industry. Stig Johan Wiklund & Carl-Fredrik Burman. Poster, PSI 2012

M&S Good Practice
Diverse Information Sources

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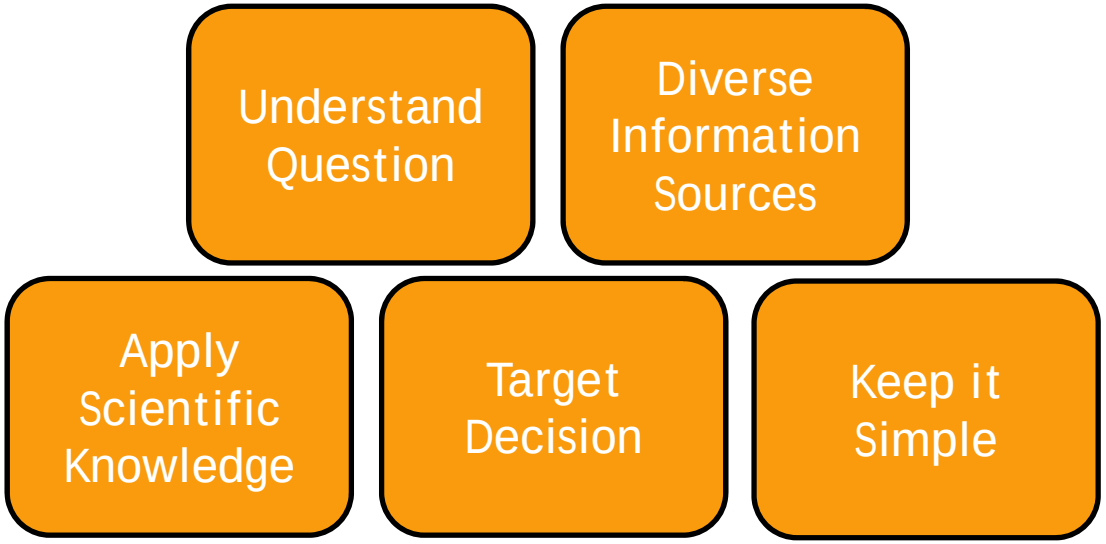
- Glean insight from where it is available



Seven theses about good modelling: some reflections on modelling and simulation in the pharmaceutical industry. Stig Johan Wiklund & Carl-Fredrik Burman. Poster, PSI 2012

M&S Good Practice Communication

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- Share ideas & methods with other quantitative scientists
- Present solution, confidence intervals, assumptions, robustness checks

Seven theses about good modelling: some reflections on modelling and simulation in the pharmaceutical industry. Stig Johan Wiklund & Carl-Fredrik Burman. Poster, PSI 2012

M&S Good Practice Continuous

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- Re-use, update and re-apply models in continuous integrated process

Seven theses about good modelling: some reflections on modelling and simulation in the pharmaceutical industry. Stig Johan Wiklund & Carl-Fredrik Burman. Poster, PSI 2012

Target Decision

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- Is an effect present? e.g. 15 % improvement in mean over placebo
- Is an effect sufficient to justify further investment?
- Which dose should be studied next?

Enhanced Quantitative Decision Making - Reducing the Likelihood of Incorrect Decisions.
Mike K Smith, J French, MM Hutmacher, KG Kowalski, & W Ewy. PKUK 2011

What to Simulate? Target Decision

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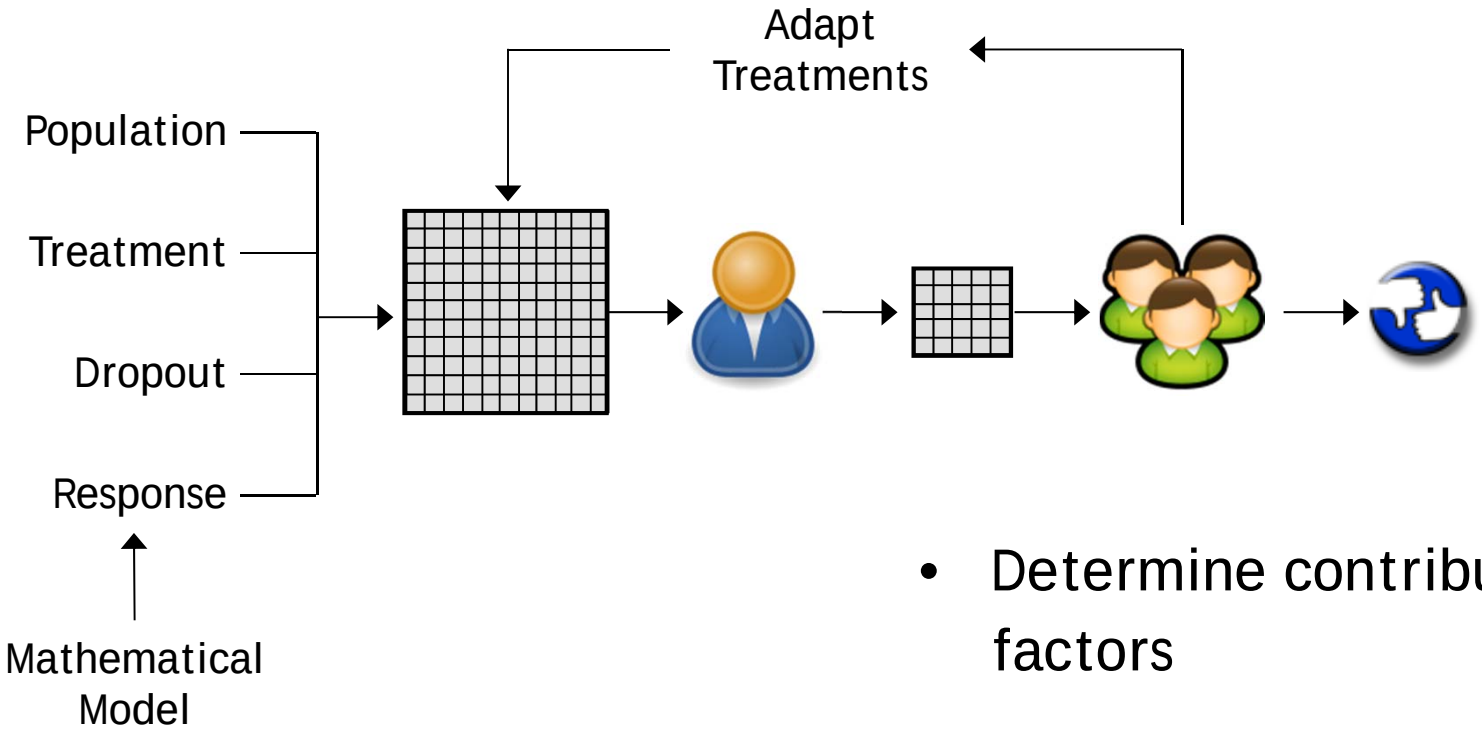

- Determine contributing factors

Using MSToolkit

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- An R package to:
  - Simulate clinical trials
  - Evaluate designs
  - Analyse methodology
  - Quantify operating characteristics
  - Apply dose and study level decision criteria

Using MSToolkit Features

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- Backed by Mango (validated, tests)
- Functionality:
  - Low level functions to perform basic tasks
  - High level functions to run then tweak
- Uses cluster (if available) to enhance performance
- Can use SAS (if available) for analysis

Using MSToolkit Facilitates Communication

MANGOSOLUTIONS
data analysis that delivers

- Developed by Mango & Pfizer in 2008, freely available
  - CRAN e.g. http://stat.ethz.ch/CRAN/
  - R Forge https://r-forge.r-project.org/projects/mstoolkit/
- Facilitate communication between M&S team
- Intuitive naming conventions facilitate communication with non-expert stakeholders

Using MSToolkit
Target Decision

MANGOSOLUTIONS
data analysis that delivers

- Suite of low level functions – select elements needed
  - Generate possible treatments `createTreatments`
  - Allocate subjects to treatments `allocateTreatments`
  - Generate parameters `createParameters`
  - Generate covariates `createCovariates`
  - Add missingness `createMCAR`
  - Add dropout `createDropout`
  - Allocate subjects to interims `createInterims`
  - Generate responses `createResponse`

Using MSToolkit
Generate Treatments

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data analysis that delivers

```
> seqMat                                    # dosing schedules
     [,1] [,2] [,3]
[1,]    0   15   30
[2,]   15   30    0
[3,]   30    0   15
> allTrts <- createTreatments(sequence = seqMat)
> allTrts
  TRT TIME DOSE
1   1    1    0
2   1    2   15
3   1    3   30
4   2    1   15
5   2    2   30
6   2    3    0
7   3    1   30
8   3    2    0
9   3    3   15
```

Using MSToolkit
Allocate Treatments

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```
> allocTrts <- allocateTreatments(trts = 3,
+     subjects = 20, prop = c(0.2, 0.2, 0.6))
> head(allocTrts)
 SUBJ TRT
1    1   3
2    2   1
3    3   3
4    4   3
5    5   3
6    6   3

> idTrts <- merge(allocTrts, allTrts)
> head(idTrts, 3)
 TRT SUBJ TIME DOSE
1   1    2    2   15
2   1    2    1    0
3   1    2    3   30
```

Using MSToolkit
Generate Covariates

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data analysis that delivers

```
> idCov <- createContinuousCovariates(subjects = 20,
+     names = c("AGE", "BMI"), mean = c(35, 24),
+     covariance = c(30, 15), digits = c(0, 1),
+     range = "18 <= AGE <= 55, 17 <= BMI <= 33")
> head(idCov)                                  # describe covariates
 SUBJ AGE  BMI
1    1  31 28.0
2    2  32 28.3
3    3  34 26.1
4    4  34 27.4
5    5  31 24.0
6    6  38 21.7

> idTrts <- merge(idTrts, idCov)
```

Using MSToolkit
Creating Parameters

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```
> ePars <- createNormalParameters(subjects = 20,
+     names = "E0, D50, EMAX", mean = c(100, 40, -70),
+     covariance = c(10, 12, 15), betNames = "D50, EMAX",
+     betCov = 8, errStruc = "Additive", digits = 1)
> head(ePars, 3)
 SUBJ   E0  D50  EMAX PAROMIT
1    1 97.1 40.2 -68.1       0
2    2 97.1 39.4 -64.7       0
3    3 97.1 39.3 -66.6       0

> idTrts <- merge(idTrts, ePars)
> head(idTrts)
 SUBJ TRT TIME DOSE AGE  BMI   E0  D50  EMAX PAROMIT
1    1   3    3   15  31 28.0 97.1 40.2 -68.1       0
2    1   3    1   30  31 28.0 97.1 40.2 -68.1       0
3    1   3    2    0  31 28.0 97.1 40.2 -68.1       0
4    2   1    2   15  32 28.3 97.1 39.4 -64.7       0
5    2   1    1    0  32 28.3 97.1 39.4 -64.7       0
6    2   1    3   30  32 28.3 97.1 39.4 -64.7       0
```

Using MSToolkit
Response & Residual Error

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```
> respData <- createResponse(data = idTrts, covariance = 35,
+     equation = "E0 + (EMAX * DOSE) / (D50 + DOSE)",
+     errStruc = "Additive", range = "RESP > 0")
> allData <- cbind(idTrts, respData)
> head(allData[-(5:6)])
  SUBJ TRT TIME DOSE   E0  D50  EMAX PAROMIT   RESP RESPOMIT
1    1   3    3   15 97.1 40.2 -68.1       0 79.751        0
2    1   3    1   30 97.1 40.2 -68.1       0 72.709        0
3    1   3    2    0 97.1 40.2 -68.1       0 95.252        0
4    2   1    2   15 97.1 39.4 -64.7       0 70.173        0
5    2   1    1    0 97.1 39.4 -64.7       0 89.553        0
6    2   1    3   30 97.1 39.4 -64.7       0 69.205        0
```

Using MSToolkit
Create a Single Trial

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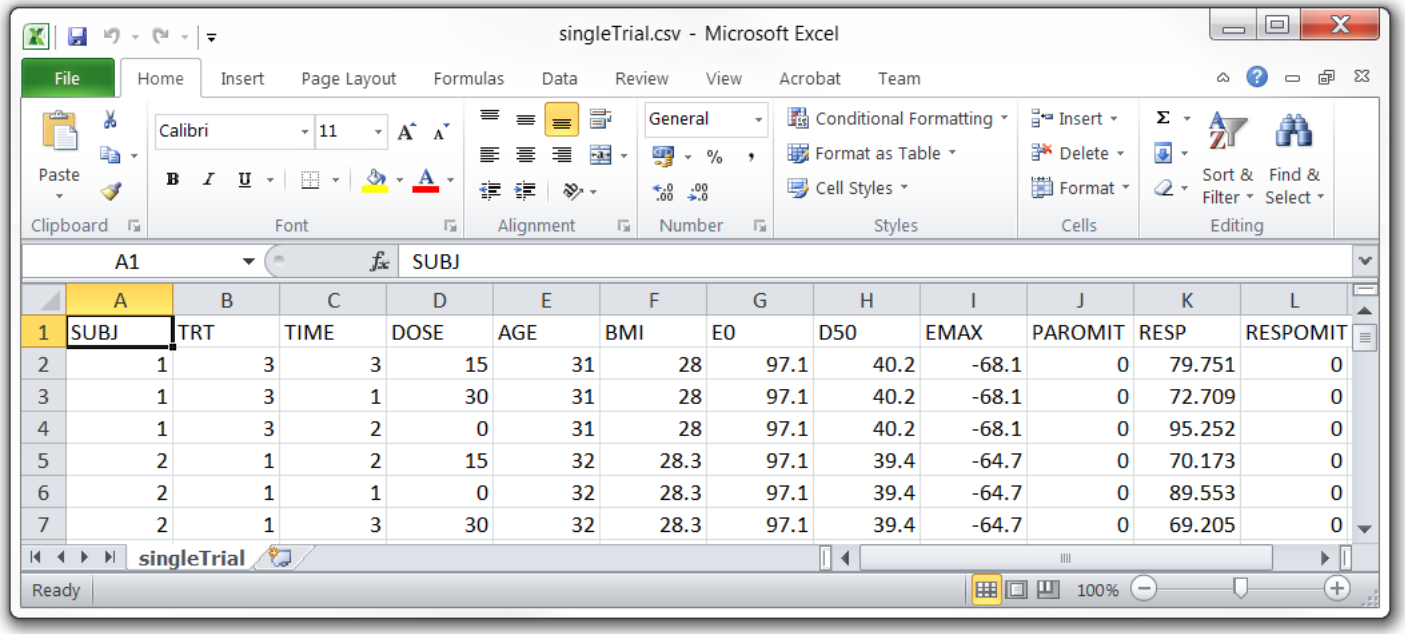

	A	B	C	D	E	F	G	H	I	J	K	L
1	SUBJ	TRT	TIME	DOSE	AGE	BMI	E0	D50	EMAX	PAROMIT	RESP	RESPOMIT
2	1	3	3	15	31	28	97.1	40.2	-68.1	0	79.751	0
3	1	3	1	30	31	28	97.1	40.2	-68.1	0	72.709	0
4	1	3	2	0	31	28	97.1	40.2	-68.1	0	95.252	0
5	2	1	2	15	32	28.3	97.1	39.4	-64.7	0	70.173	0
6	2	1	1	0	32	28.3	97.1	39.4	-64.7	0	89.553	0
7	2	1	3	30	32	28.3	97.1	39.4	-64.7	0	69.205	0

Using MSToolkit
Or use High Level Function

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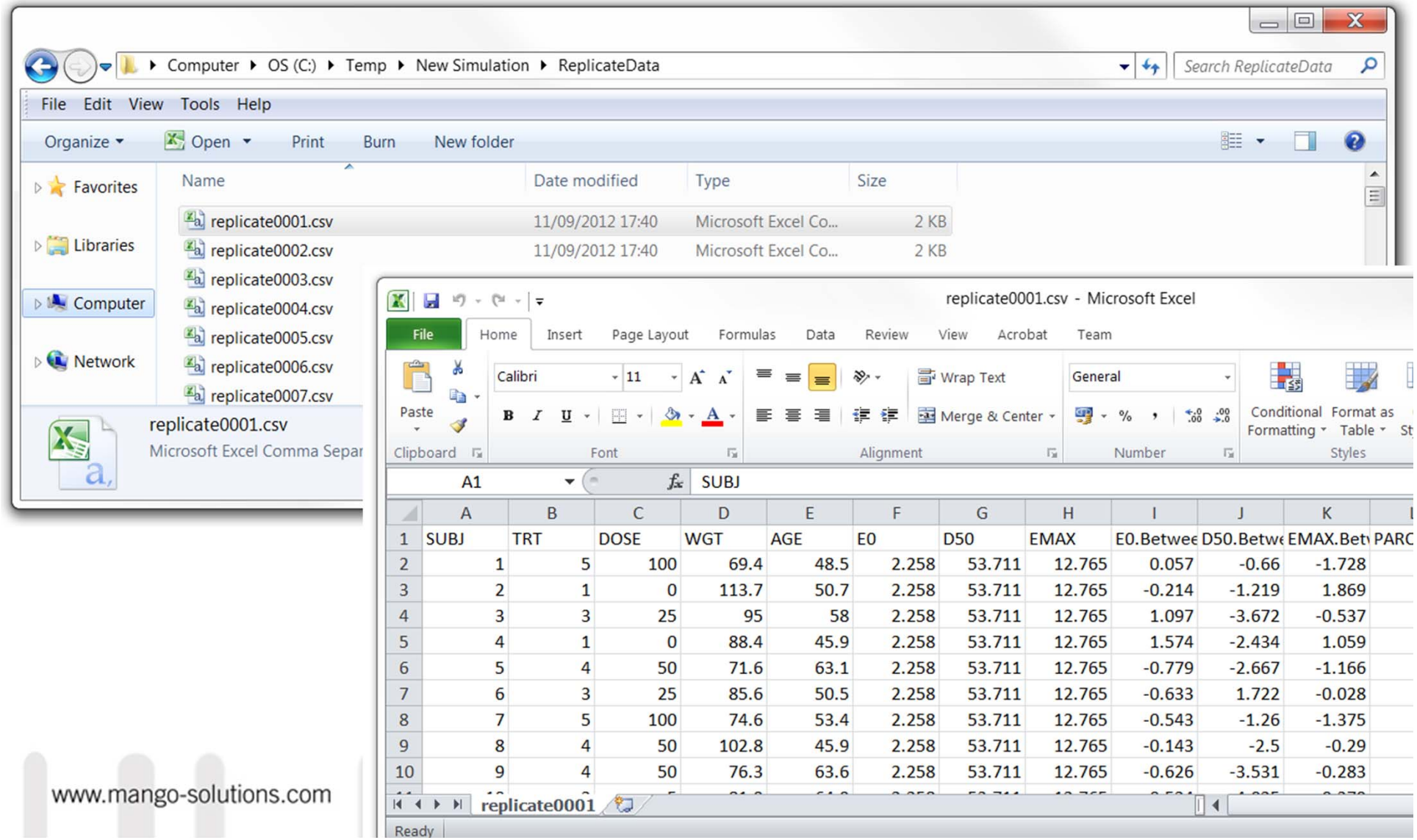
data analysis that delivers

```
> generateData(replicateN = 100, subjects = 20,
+     workingPath = "C:/Temp/New Simulation",
+     treatDoses = c(0, 5, 25, 50, 100),
+     conCovNames = c("WGT", "AGE"), conCovMean = c(83, 55),
+     conCovVCov = c(13, 9)^2 , conCovDigits = 1,
+     conCovCrit = "18 <= AGE <= 65",
+     genParNames = "E0, D50, EMAX", genParMean = c(2, 50, 10),
+     genParVCov = diag(c(0.5, 30, 10)),
+     genParBtwNames = "E0, D50, EMAX", genParBtwMean = c(0, 0, 0),
+     genParBtwVCov = diag(c(0.4, 5, 2)),
+     respEqn = "E0 + (DOSE * EMAX) / (DOSE + D50)",
+     respVCov = 5,
+     interimSubj = "0.3, 0.7")
```

Using MSToolkit To Generate Replicates

MANGOSOLUTIONS
data analysis that delivers



	A	B	C	D	E	F	G	H	I	J	K
1	SUBJ	TRT	DOSE	WGT	AGE	E0	D50	EMAX	E0.Betwee	D50.Betwe	EMAX.Betv
2	1	5	100	69.4	48.5	2.258	53.711	12.765	0.057	-0.66	-1.728
3	2	1	0	113.7	50.7	2.258	53.711	12.765	-0.214	-1.219	1.869
4	3	3	25	95	58	2.258	53.711	12.765	1.097	-3.672	-0.537
5	4	1	0	88.4	45.9	2.258	53.711	12.765	1.574	-2.434	1.059
6	5	4	50	71.6	63.1	2.258	53.711	12.765	-0.779	-2.667	-1.166
7	6	3	25	85.6	50.5	2.258	53.711	12.765	-0.633	1.722	-0.028
8	7	5	100	74.6	53.4	2.258	53.711	12.765	-0.543	-1.26	-1.375
9	8	4	50	102.8	45.9	2.258	53.711	12.765	-0.143	-2.5	-0.29
10	9	4	50	76.3	63.6	2.258	53.711	12.765	-0.626	-3.531	-0.283

Using MSToolkit Data Output

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data analysis that delivers

```
> getEctdDataMethod()
[1] "Internal"

> setEctdDataMethod("CSV")
```

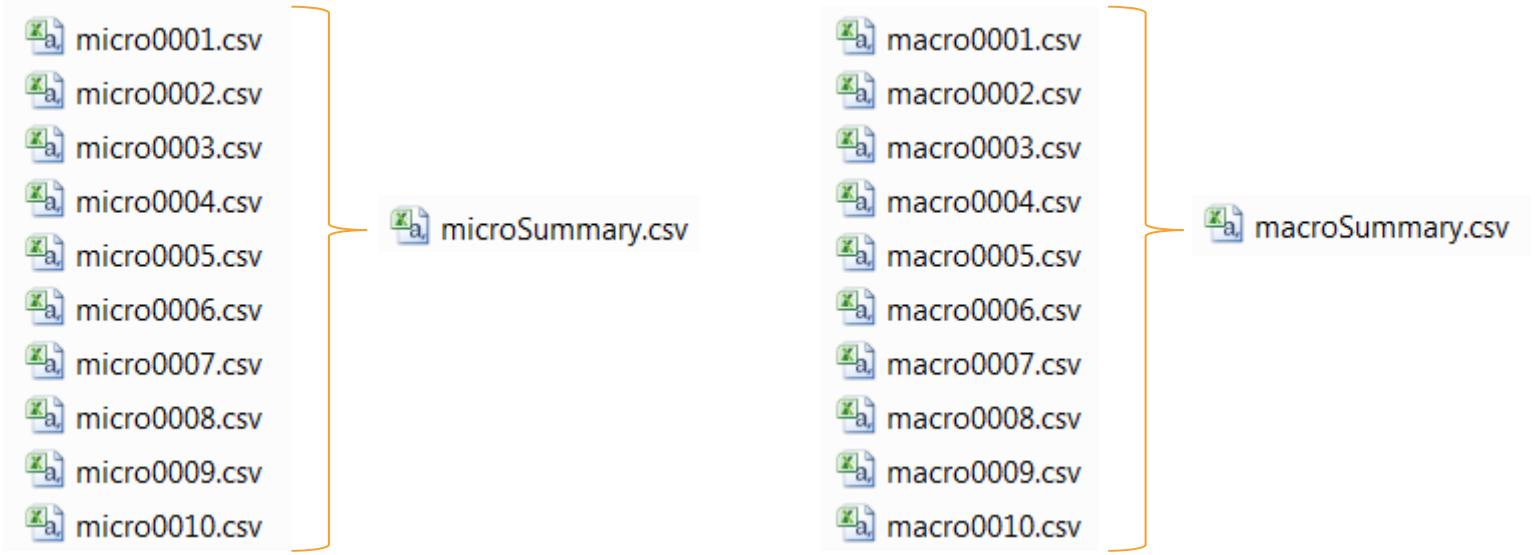
- Text files (csv)
- Data files (RData)
- Retained internally in memory for increased speed

Using MSToolkit
Analyze Data

MANGOSOLUTIONS
data analysis that delivers

```
> meanFun <- function(data) { as.data.frame(t(data$MEAN)) }

> analyzeData(analysisCode = parallel,
+      macroCode = meanFun,
+      grid = FALSE)
```



Apply Scientific Knowledge

MANGOSOLUTIONS
data analysis that delivers

- Preclinical information about this drug
- Incorporate description of disease
- Competitor or literature information about other drugs in class

Target Decision
Quantitative Go/No Go

MANGOSOLUTIONS
data analysis that delivers

```
> macrocode <- function(data, Threshold = -3.2) {
+     out <- data$LOWER > Threshold
+     out <- as.data.frame(t(out))
+     names(out) <- paste("GO", data$DOSE, sep = "")
+     return(out)
+ }
```

- Go if lower confidence interval of response is greater than threshold response -3.2

Informing Decisions
Prior Information

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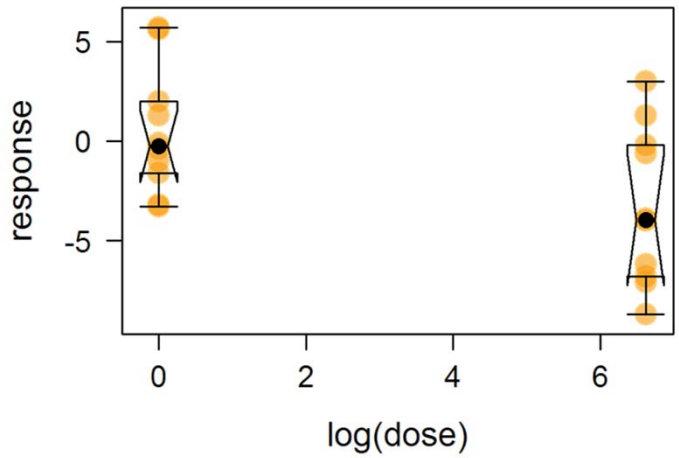
```
> group <- rep(c(0, log(750)), each = 10)
> placebo <- c(-1.6, 1.3, 5.7, -0.1, -3.3, -1, 5.6, 2, -0.4, -3.2)
> active <- c(-7.1, -8.7, -6.8, 1.3, -0.6, 3, -3.9, -6.2, -4, -0.2)
> response <- c(placebo, active)
```

```
> xyplot(response ~ group,
+     panel = customPanel,
+     axis = axis.smart,
+     xlab = "log(dose)",
+     xlim = c(-0.5, 7))
```

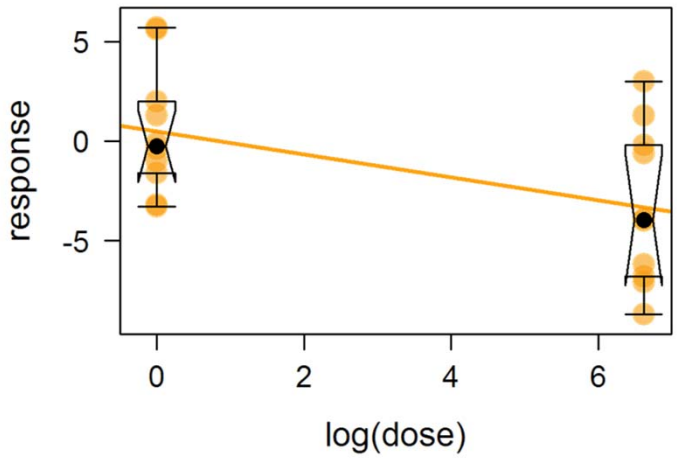


Informing Decisions
Estimate Parameters

MANGOSOLUTIONS
data analysis that delivers

```
> mod <- lm(response ~ group)
> sumMod <- summary(mod)
> coefMod <- coef(mod)
> varMod <- sumMod$sigma^2
> vcov <- varMod * sumMod$cov    # scaled varcov matrix

> xyplot(response ~ group,
+      panel = lmCustomPanel,
+      coef = coefMod,
+      axis = axis.smart,
+      xlab = "log(dose)",
+      xlim = c(-0.5, 7))
```



Informing Decisions
Define Analysis

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data analysis that delivers

```
> parallel <- function(data) {
+     analys <- lm(RESP ~ log(DOSE), data = data)
+     sumAnalys <- summary(analys)
+     doses <- sort(unique(data$DOSE))
+     fitted <- predict.lm(analys, newdata = list(DOSE = doses),
+         se.fit = TRUE, interval = "confidence", level = 0.95)
+
+     mn <- fitted$fit[, 1]
+     n <- tapply(data$RESP, list(data$DOSE), length)
+     INTER <- unique(data$INTER)
+     SLOPE <- unique(data$SLOPE)
+     TRUTH <- INTER + SLOPE * log(doses)
+
+     outDf <- data.frame(
+         DOSE = doses, MEAN = mn, SE = fitted$se.fit,
+         LOWER = fitted$fit[, 2], UPPER = fitted$fit[, 3],
+         N = n, TRUTH = TRUTH, INTER = INTER, SLOPE = SLOPE)
+     return(outDf)
+ }
```

Informing Decisions
Simulate Data

MANGOSOLUTIONS
data analysis that delivers

```
> getEctdDataMethod()
[1] "Internal"

> generateData(replicateN = 500,
+     subjects = 60, treatSubj = rep(10, 6),
+     treatDoses = c(0.1, 5, 20, 75, 250, 750),
+     genParNames = "INTER, SLOPE",
+     genParMean = as.vector(coefMod),
+     genParVCov = vcov,
+     respEqn = "INTER + SLOPE * log(DOSE)",
+     respVCov = varMod,
+     seed = 344860)
```

Informing Decisions
Visualise Data

MANGOSOLUTIONS
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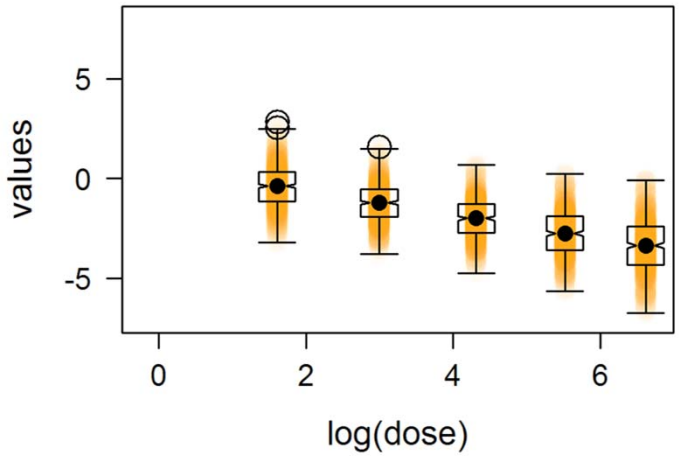
```
> analyzeData(analysisCode = parallel,
+     macroCode = function(data) { as.data.frame(t(data$MEAN)) },
+     grid = FALSE)

> dataSum <- read.csv("macroSummary.csv")
> doses <- sort(unique(.ectdEnv$DataStore[[1]]$DOSE))
> dataStack <- stack(dataSum,
+      select = -Replicate)
> dataStack$ind <- log(doses)[dataStack$ind]

> xyplot(values ~ ind, dataStack,
+     panel = customPanel,
+     axis = axis.smart,
+     xlab = "log(dose)",
+     xlim = c(-0.5, 7))
```



Informing Decisions
Analyze Data

MANGOSOLUTIONS
data analysis that delivers

```
> analyzeData(analysisCode = parallel,
+     macroCode = macrocode, grid = FALSE)

> datasum <- read.csv("macroSummary.csv")

> apply(datasum[-1], 2, mean)
G00.1   G05  G020  G075 G0250 G0750
0.966 0.954 0.844 0.562 0.278 0.114
```

Informing Decisions

MANGOSOLUTIONS
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- Design a trial and simulate data
- Compare performance metrics with deterministic outcome
- Characterise probability of making correct/incorrect decision using:
  - statistical significance & Type I/Type II errors or
  - reference to clinical decision efficacy or tolerability

Communication
Demonstrate Alternatives

MANGOSOLUTIONS
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- What if data generating process is nonlinear but the data are analysed using a linear model?
- Examine robustness when assumptions change compared to initial assumptions

Conclusion

MANGOSOLUTIONS
data analysis that delivers

- Good Practice during M&S will make it easier to support submission
- MSToolkit provides:
  - quick to learn & easily shared data generation tools
  - a reusable but flexible framework for analysing systems to inform go/no go decisions

Acknowledgements

- Rich Pugh (Mango Solutions)
- Mike Smith (Pfizer)
- Stig Johan Wiklund (Astrazeneca)
- Carl-Fredrik Burman (Astrazeneca)

References

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Current Position and Expectation for use of M&S in Drug Development and Regulatory Decision Making. Peter A Milligan. Parallel 2c, PSI 2012

Role of Modelling and Simulation in Regulatory Decision Making in Europe. Terry Shepard. Parallel 2c, PSI 2012

Seven theses about good modelling: some reflections on modelling and simulation in the pharmaceutical industry. Stig Johan Wiklund & Carl-Fredrik Burman. Poster, PSI 2012

Enhanced Quantitative Decision Making - Reducing the Likelihood of Incorrect Decisions. Mike K Smith, J French, MM Hutmacher, KG Kowalski, & W Ewy. PKUK 2011

PSI M&S SIG Software Hands on Session. Mike K Smith. 17th November 2010

Basel R
http://www.baselr.org/

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- Date: Thursday 13th September
- Time: 6.30 pm (presentations begin at 7 pm)
- Venue: transBarent, Viaduktstrasse 3, Basel 4051
- Presentations:
  - Calling R from .NET: a case-study using Rapid NCA, the non-compartmental analysis workflow tool
    - Chris Campbell
  - R as the weapon of choice for a simulation case study of a step-wedge design
    - MariaBeth Silkey

Questions

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