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Spencer Health Solutions

BASS XXVI

October 22nd 2019

Taking Adherence, PROs and RWD into Account in Clinical Trials

Joint work with Aiden Flynn, Linda Warnock at Exploristics

Outline

- Current clinical trial challenges
- Estimands
- Quantifying the impact of adherence/retention
- The hybrid trial
- Real world data
- Patient engagement in the home/work/travel
- Using the data

  ePRO and RWD
  Cluster analysis – Which patients are similar
  Deriving a Health Score

Pragmatic, hybrid and virtual trials

- Reduce costs and clinic visits
- Results should better reflect the real world
- Increase patient diversity
  - Location
  - Socio economic status

Patient-centricity

- Make it easy for patients to participate in trials
- Reduce patient burden
- Include patients in planning

Late-Stage Priorities

How important is it for spencer® smart hub to demonstrate the following? *Late Stage Development Respondents Only*		
Qualitative Customer Buying Factor	**Score**	**Rank**
Increased patient adherence to greater than 90%	9.1	1st
Improved data quality and integrity of results	8.9	2nd
Reduction in the number of patient dropouts	8.6	3rd
Electronic traceability	8.6	4th
Real time data to help principal investigators	8.3	5th
A more defined and clearer outcome to a clinical trial	8.2	6th
Shortened duration of a clinical study	7.8	7th
Reduction in the number of patients required for a clinical trial	7.8	8th
Reduction in clinical visits	7.4	9th
spencer® interactions: a dedicated team to help with daily adherence	7.4	10th
Test medication home delivery	7.3	11th
A reduction in visits to the doctor	7.2	12th
Encouraging messages sent to patients via spencer® to congratulate them on taking their medications	6.9	13th
Direct access for the patient to clinical team via video conference	6.8	14th
Test medication dispensed along with vitamins and other supplements	6.6	15th

Tier 1

Note: Respondents ranked each on a scale of 1-10, with 1 being the lowest score, and 10 being the highest score.

Kineticos LIFE SCIENCES CONSULTING

Estimands and Sensitivity Analysis

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 30 August 2017
2 EMA/CHMP/ICH/436221/2017
3 Committee for Human Medicinal Products

4 ICH E9 (R1) addendum on estimands and sensitivity 5 analysis in clinical trials to the guideline on statistical 6 principles for clinical trials

7 Step 2b

Transmission to CHMP	July 2017
Adoption by CHMP for release for consultation	20 July 2017
Start of consultation	31 August 2017
End of consultation (deadline for comments)	28 February 2018

Additional data are needed to gain clarity on treatment effects

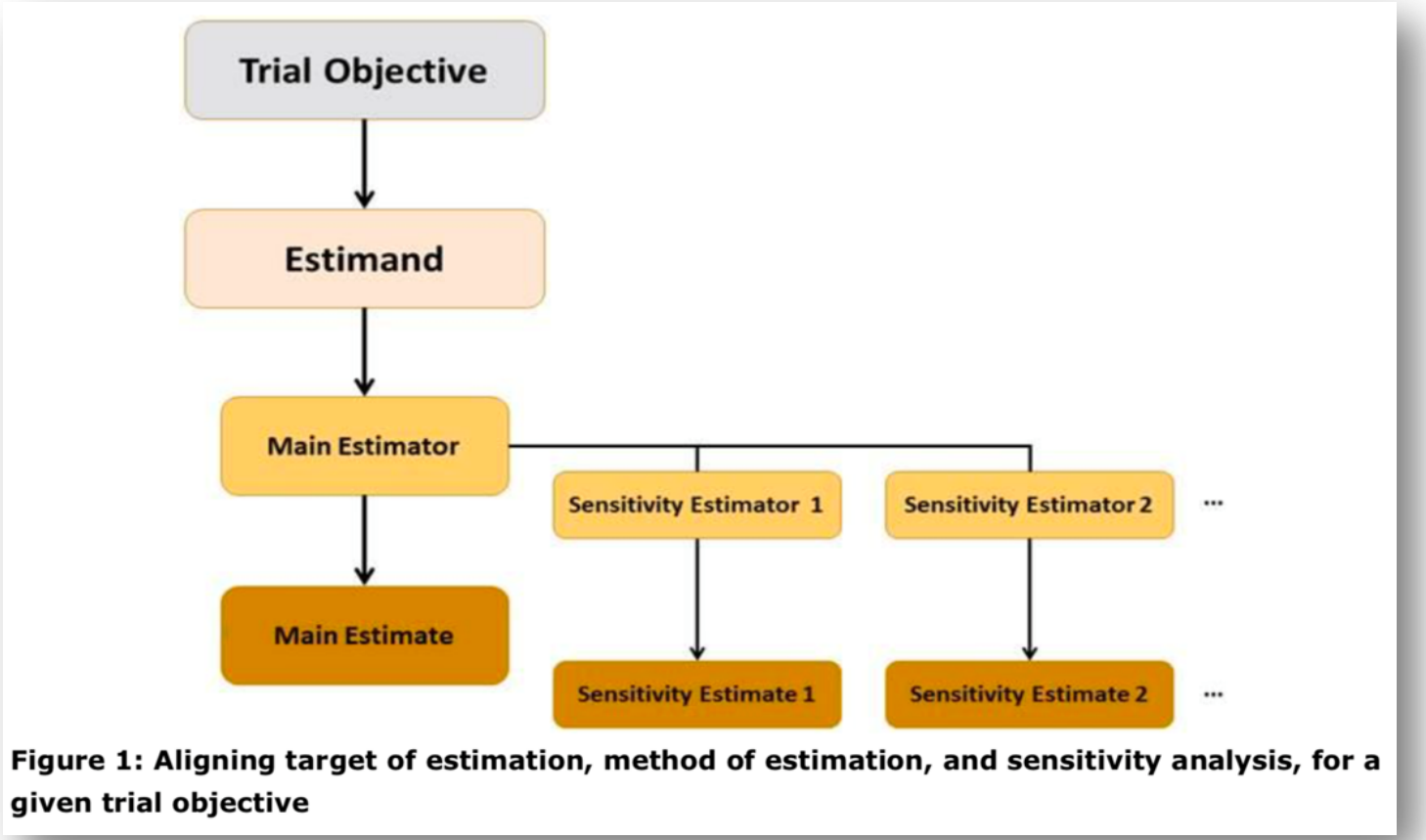


Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

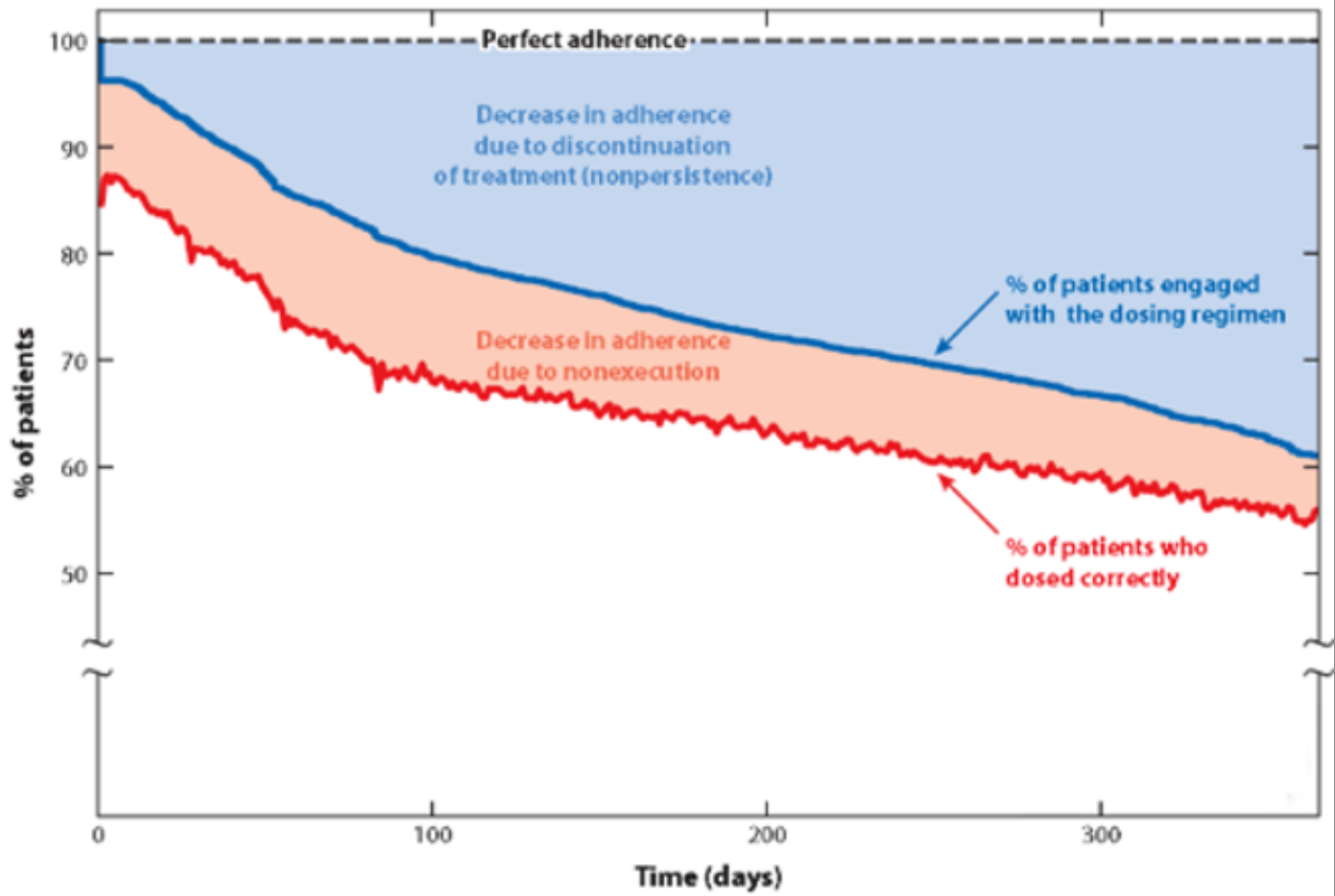
How do we obtain data that can potentially be used for sensitivity estimators?

- Adherence and persistence
- Missingness
- Changes in medications and health conditions
- Environmental factors

Clinical trials sample size calculations are often inflated in order to accommodate adherence issues and patient dropouts

- By the end of 6 months ~ 40% of patients have dropped out or are non-adherent
- To accommodate this reality, clinical teams:
  - Plan on recruiting X% more patients than would typically be needed
  - Recruit additional patients once the study ends if power is insufficient for analysis
  - Use an adaptive design approach to correct sample sizes mid-study

Figure 1: IMP nonadherence in Clinical Trials* [7]

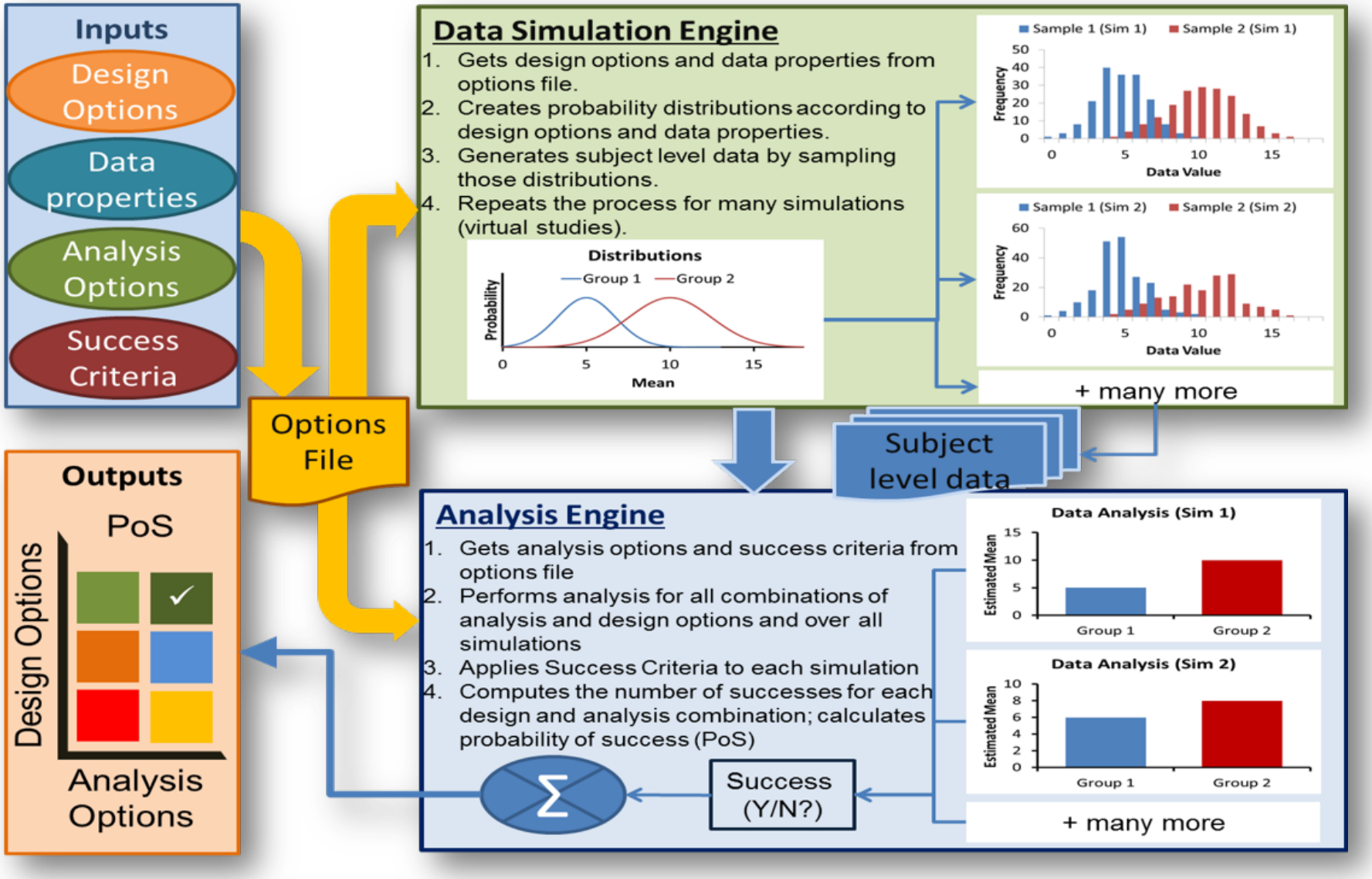


*16,907 participants derived from 95 clinical studies ranging from 30 to 1,400 days

Clinical Trials Simulations can help quantify the potential impact of adherence and persistence

- Simulation involves the use of a model to describe a process or system, executing the model, and analysing the outputs
- Simulation is useful when there are multiple, inter-related factors that impact the outputs
- Our example simulations are based on results taken from a hypertension paper
- Randomised trial of a perindopril-based blood-pressure–lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. The Lancet Vol 358 Sept 2001
- From the paper percentage of subjects with stroke over a 4-year period
- 14.4% on placebo, 8.5% on treatment
- Max window of effect = 5.9%

Kerus Cloud® Clinical Trials Simulation Environment



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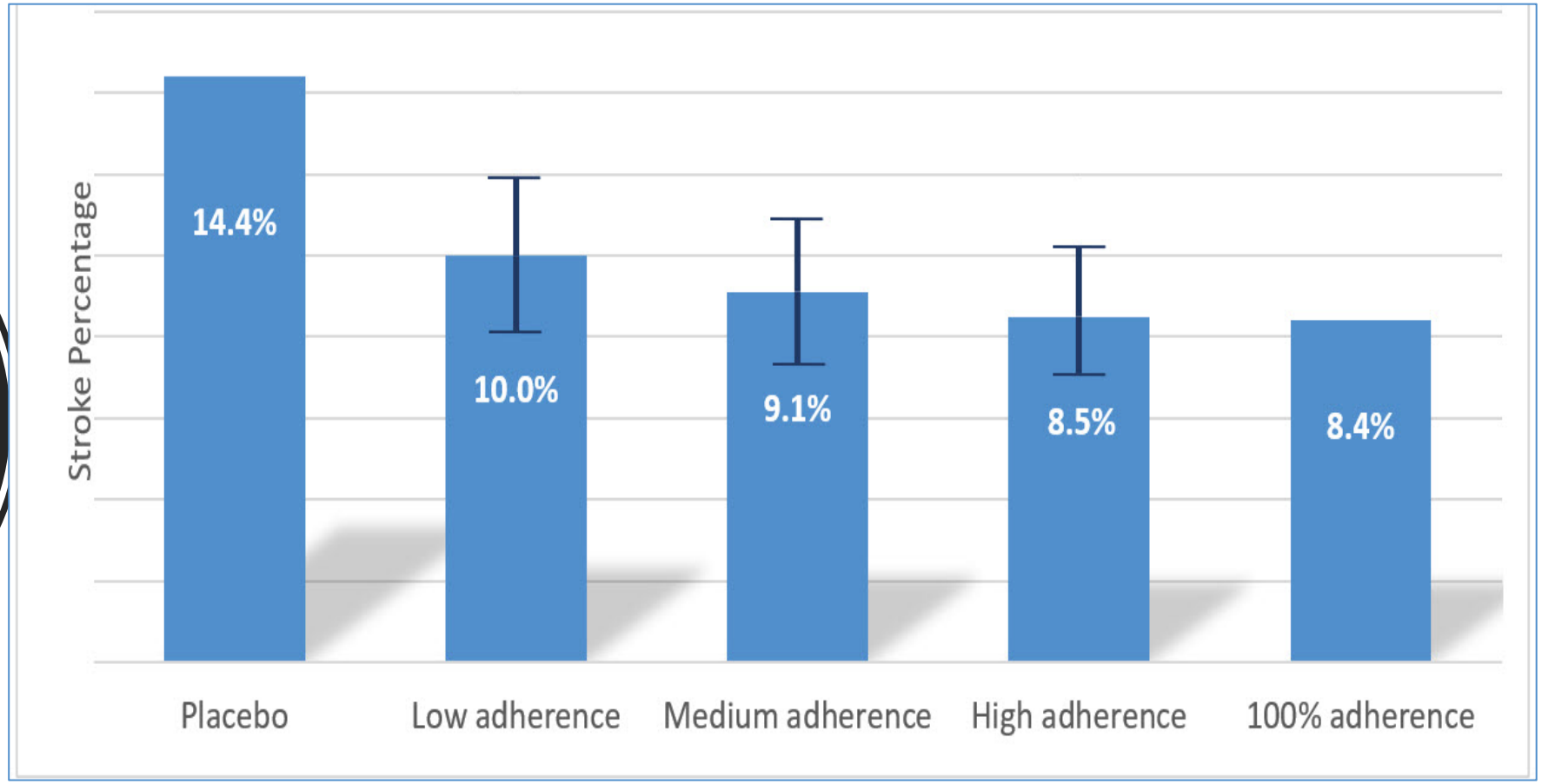
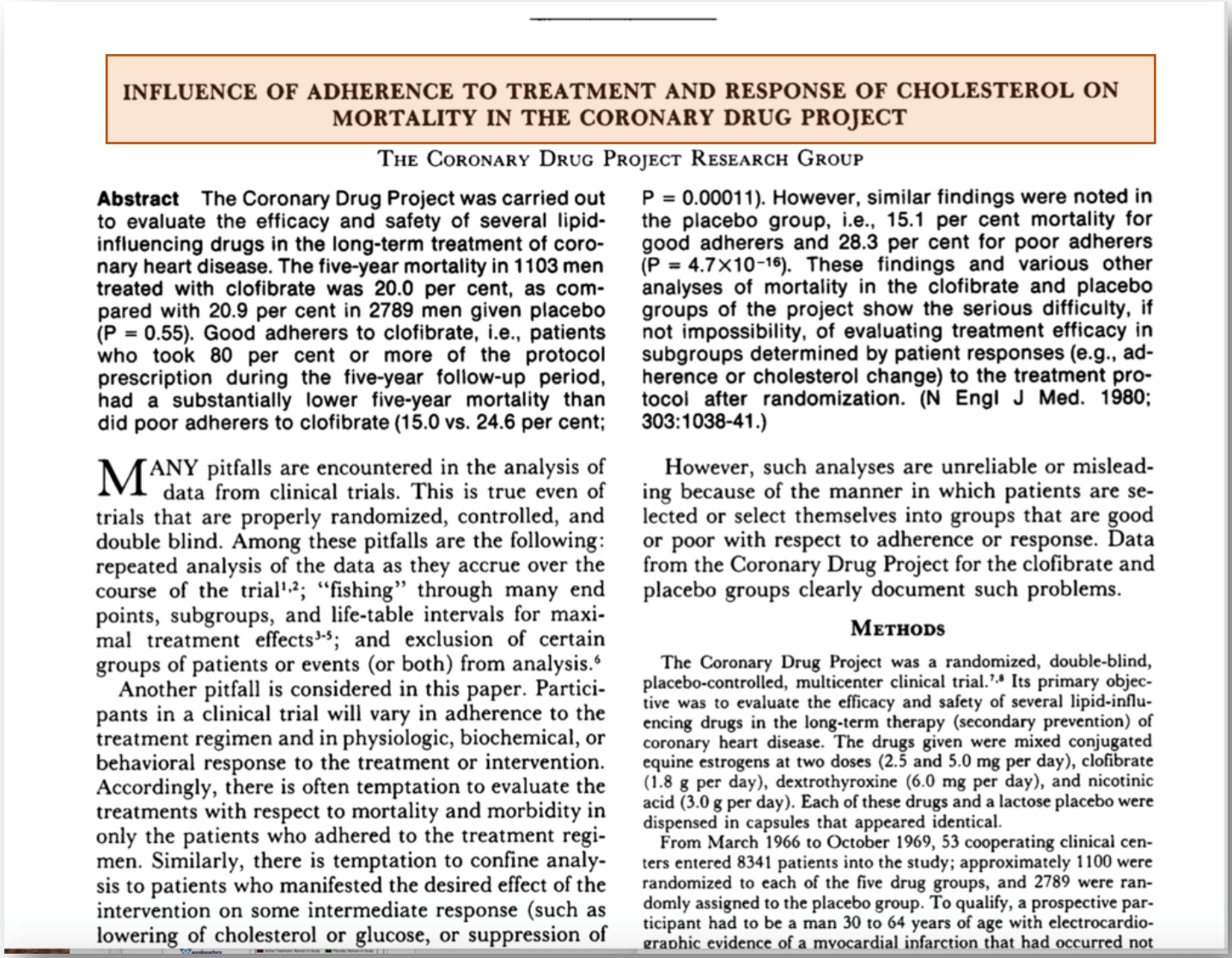
Adherence plays a major role in clinical trial outcomes



Dropouts are often related to lack of efficacy and seen in both treated and placebo arms



INFLUENCE OF ADHERENCE TO TREATMENT AND RESPONSE OF CHOLESTEROL ON MORTALITY IN THE CORONARY DRUG PROJECT

THE CORONARY DRUG PROJECT RESEARCH GROUP

Abstract The Coronary Drug Project was carried out to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term treatment of coronary heart disease. The five-year mortality in 1103 men treated with clofibrate was 20.0 per cent, as compared with 20.9 per cent in 2789 men given placebo (P = 0.55). Good adherers to clofibrate, i.e., patients who took 80 per cent or more of the protocol prescription during the five-year follow-up period, had a substantially lower five-year mortality than did poor adherers to clofibrate (15.0 vs. 24.6 per cent; P = 0.00011). However, similar findings were noted in the placebo group, i.e., 15.1 per cent mortality for good adherers and 28.3 per cent for poor adherers ($P = 4.7 \times 10^{-16}$). These findings and various other analyses of mortality in the clofibrate and placebo groups of the project show the serious difficulty, if not impossibility, of evaluating treatment efficacy in subgroups determined by patient responses (e.g., adherence or cholesterol change) to the treatment protocol after randomization. (N Engl J Med. 1980; 303:1038-41.)

MANY pitfalls are encountered in the analysis of data from clinical trials. This is true even of trials that are properly randomized, controlled, and double blind. Among these pitfalls are the following: repeated analysis of the data as they accrue over the course of the trial[1,2]; "fishing" through many end points, subgroups, and life-table intervals for maximal treatment effects[3-5]; and exclusion of certain groups of patients or events (or both) from analysis.[6]

Another pitfall is considered in this paper. Participants in a clinical trial will vary in adherence to the treatment regimen and in physiologic, biochemical, or behavioral response to the treatment or intervention. Accordingly, there is often temptation to evaluate the treatments with respect to mortality and morbidity in only the patients who adhered to the treatment regimen. Similarly, there is temptation to confine analysis to patients who manifested the desired effect of the intervention on some intermediate response (such as lowering of cholesterol or glucose, or suppression of

However, such analyses are unreliable or misleading because of the manner in which patients are selected or select themselves into groups that are good or poor with respect to adherence or response. Data from the Coronary Drug Project for the clofibrate and placebo groups clearly document such problems.

METHODS

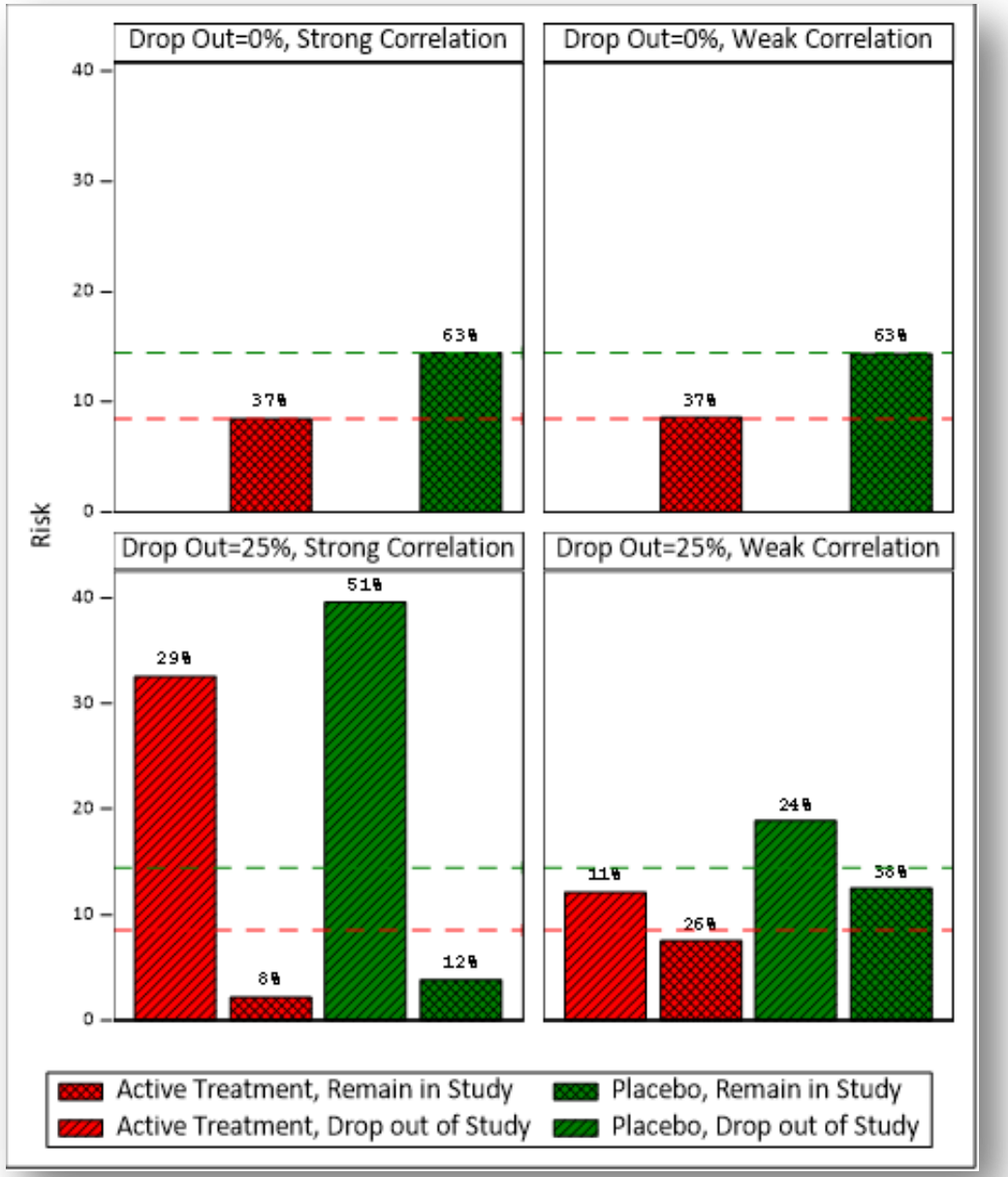
The Coronary Drug Project was a randomized, double-blind, placebo-controlled, multicenter clinical trial.[7,8] Its primary objective was to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term therapy (secondary prevention) of coronary heart disease. The drugs given were mixed conjugated equine estrogens at two doses (2.5 and 5.0 mg per day), clofibrate (1.8 g per day), dextrothyroxine (6.0 mg per day), and nicotinic acid (3.0 g per day). Each of these drugs and a lactose placebo were dispensed in capsules that appeared identical.

From March 1966 to October 1969, 53 cooperating clinical centers entered 8341 patients into the study; approximately 1100 were randomized to each of the five drug groups, and 2789 were randomly assigned to the placebo group. To qualify, a prospective participant had to be a man 30 to 64 years of age with electrocardiographic evidence of a myocardial infarction that had occurred not

Simulation Scenarios

A range of scenarios were simulated based on combinations of the following:

Adherence levels	Full adherence, no drop out (High)
	70% subjects adherent 50% of the time (Low)
Persistence	Complete
	25% drop out (equivalent to a 12-month study)
Correlation between likelihood of drop out and likelihood of stroke	High (correlation=0.4)
	Low (correlation=0.1)
	Positive correlation:patient is more likely to drop out with poor response



Labels (%) indicate the proportion of the overall stroke population in the group of interest

Estimated impact non-persistence on stroke risk (high adherence)

- When the risk of drop-out is correlated with poor response, the risk of stroke falls in patients remaining in the study.
- This effect is considerable when there is a strong correlation
- This leaves a smaller proportion of the stroke population remaining in the study

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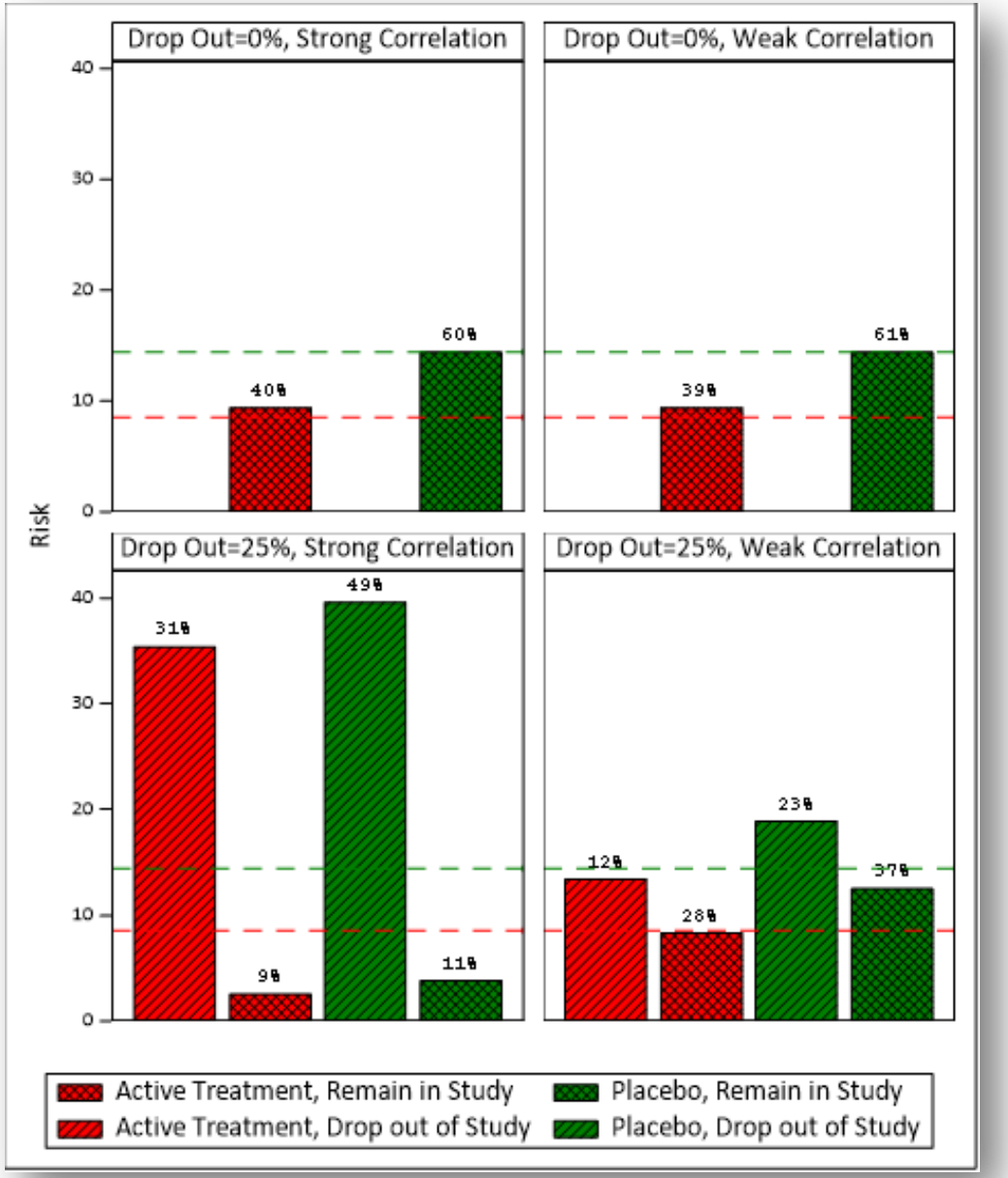

Labels (%) indicate the proportion of the overall stroke population in the group of interest

Estimated impact of persistence on stroke risk (low adherence)

- A similar pattern is observed in the high adherence group
- One difference is the higher risk of stroke in the active group.
  - The difference between the risk of stroke in placebo versus active is reduced
- When the correlation is strong, 80% of the stroke population drops out
- This compares with 35% when the correlation is weak

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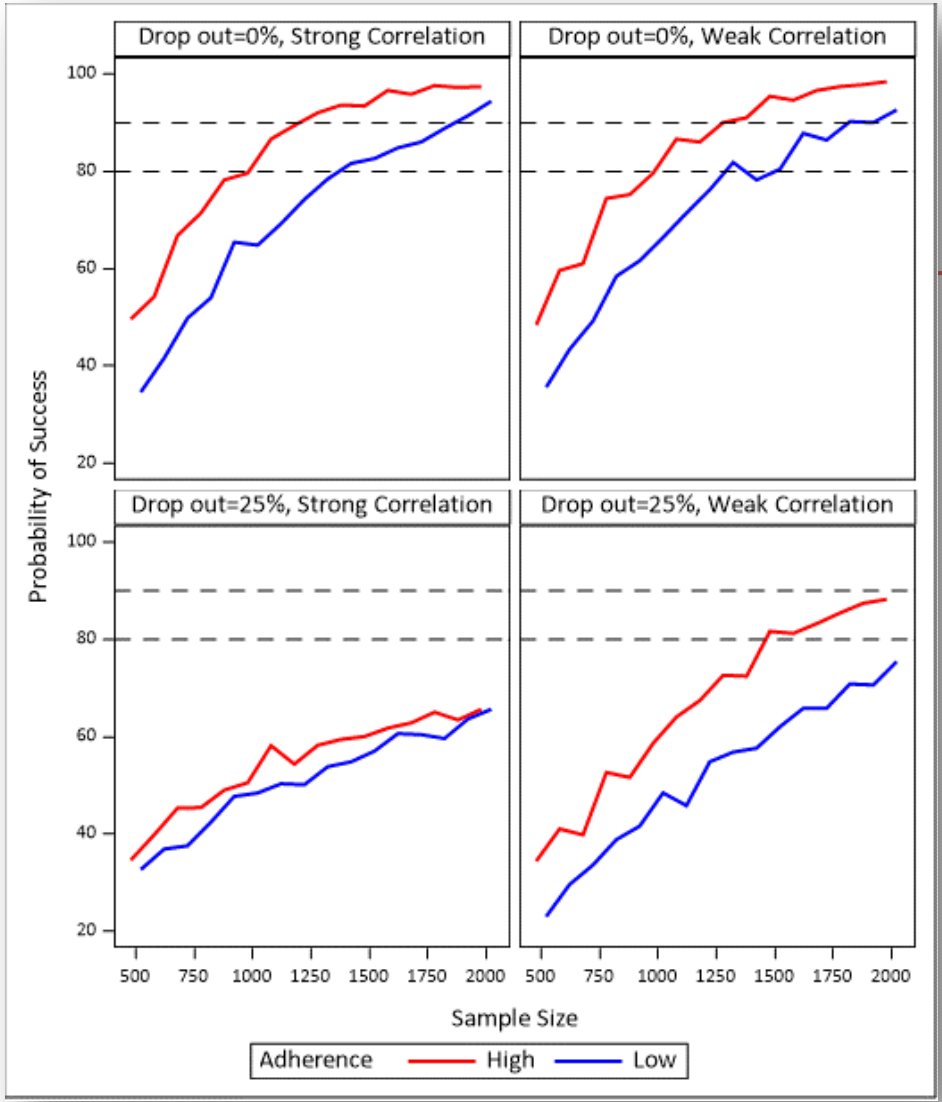
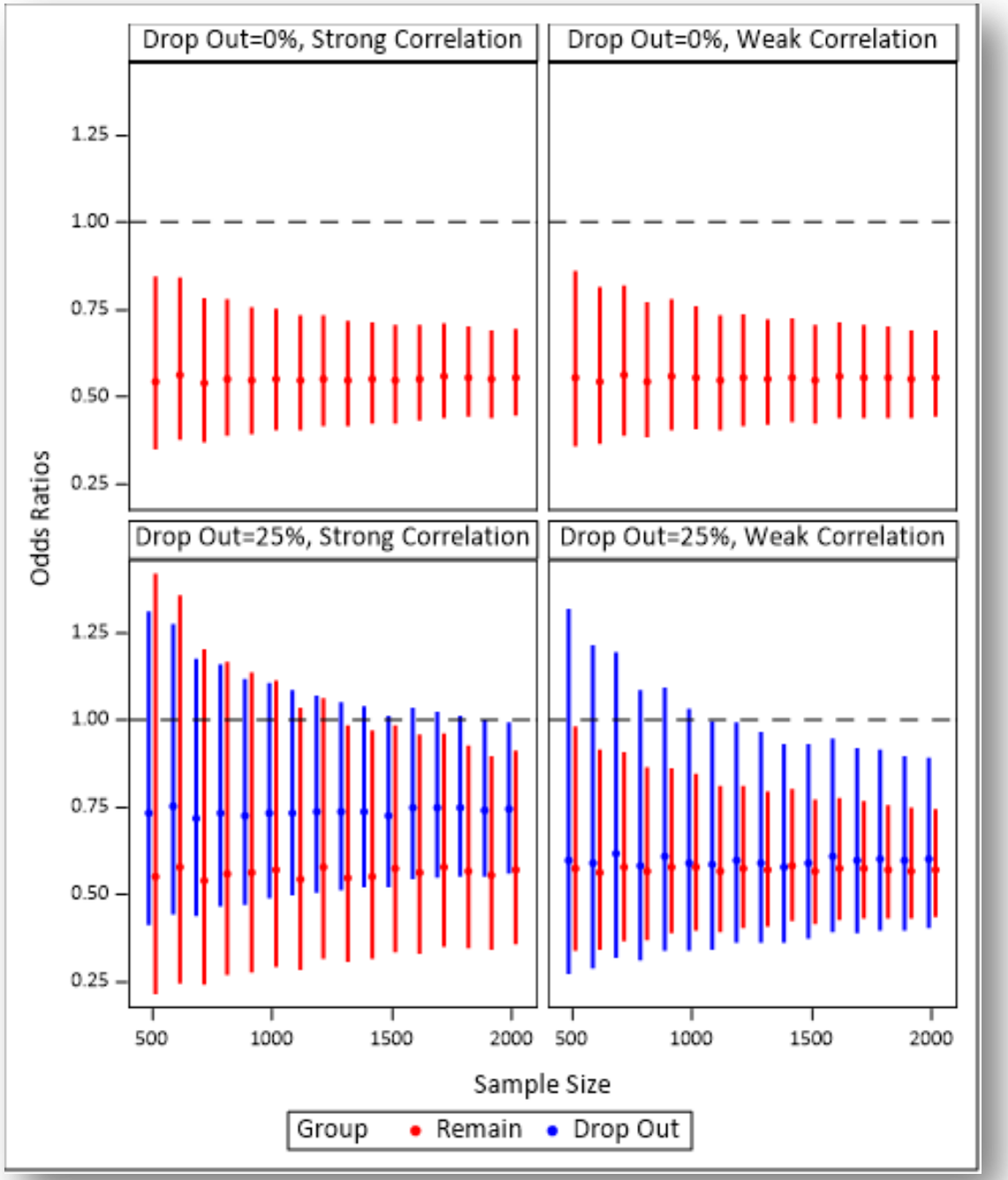


Impact on probability of success (study power)

- The probability of success increases markedly with sample size and level of adherence
- Where there is a correlation between the risk of drop out and the risk of stroke (i.e. poor response) the statistical power reduces
- Non-persistence correlation with poor adherence does not achieve the required statistical power for any scenario evaluated



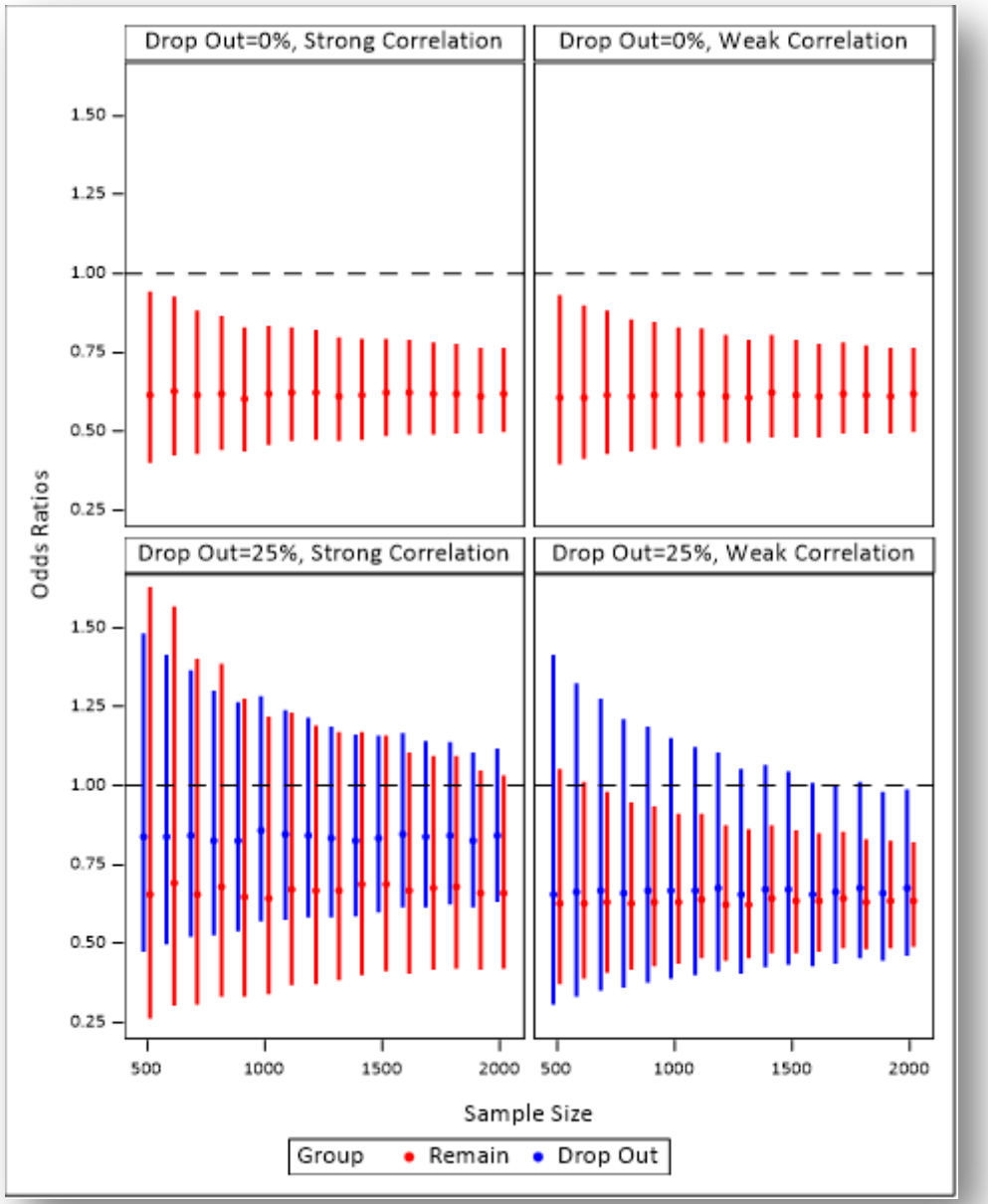
Understanding study power (high adherence)

- Where there is a **strong correlation** between the risk of drop out and stroke, the Odds Ratio **confidence intervals increase** in the **subjects remaining in the study.**

- Likewise, the estimate of the odds ratio is **biased** as the effects of patients dropping out are not evenly distributed across treatment groups
  - Treatment response in the placebo group is better than expected, underestimating the stroke risk

- When the **correlation is weak**, the increase in confidence intervals in the remain group is much smaller and the **bias is reduced**

- Therefore, the **study power** is decreased when the **correlation is stronger**.



Understanding study power (low adherence)

- Where there is a **strong correlation** between the **risk of drop out and stroke**, the **confidence intervals increase markedly in the group of subjects that remain on the study.**

- Likewise, the estimate of the odds ratio is **biased as the effects of patients dropping out are not evenly distributed across treatment groups**

- Treatment response in the placebo group is better than expected, **underestimating the stroke risk**

- When the **correlation is weak**, the increase in confidence intervals in the remain group is much smaller, and the **bias is reduced**

Adherence/Persistence Simulation Summary

- Simulation was developed to estimate the impact of non-adherence and persistence (drop-outs).
- Estimated the impact of adherence and non-persistence when correlated with poor response (in this instance, higher risk of stroke).
- The inter-relationships between these factors is complex.
- Non-adherence and non-persistence has a dramatic impact on the success of a clinical trial.
- This leads to a significant reduction in study power or a large increase in the study size to compensate for the reduction in power.

When non-persistence is linked with lack of efficacy then the observed treatment response is biased because non-responders are more likely to drop out

This leads to an over-estimation of treatment response
This has a disproportionate effect on the placebo arm leading to an inflated placebo response

Real World Data

- Available across a large population
- Provide additional insights
- Useful for disease studies

- Not well controlled
- Bias can muddy the waters
- Often contradictory

Uses for real world data (RWD) in clinical studies

ePROs and surveys can be used as endpoints

See BASS 2018 Cappelleri tutorial

RDW can also be combined to create supporting evidence

Pain scores, Quality of life

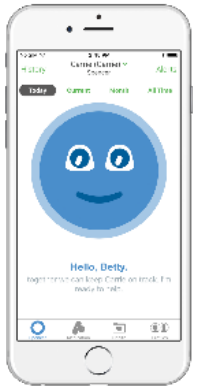
RDW can be used to monitor patients over time

Real World Data can be collected anywhere!

spencer health solutions

Technology to the Rescue!

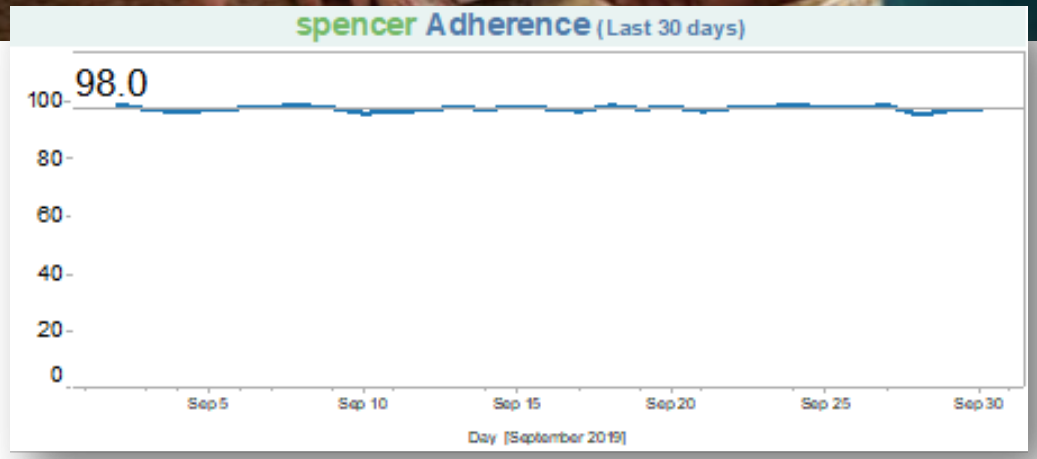
Participant



On Participant's Mobile Device

With Participant's Care Team

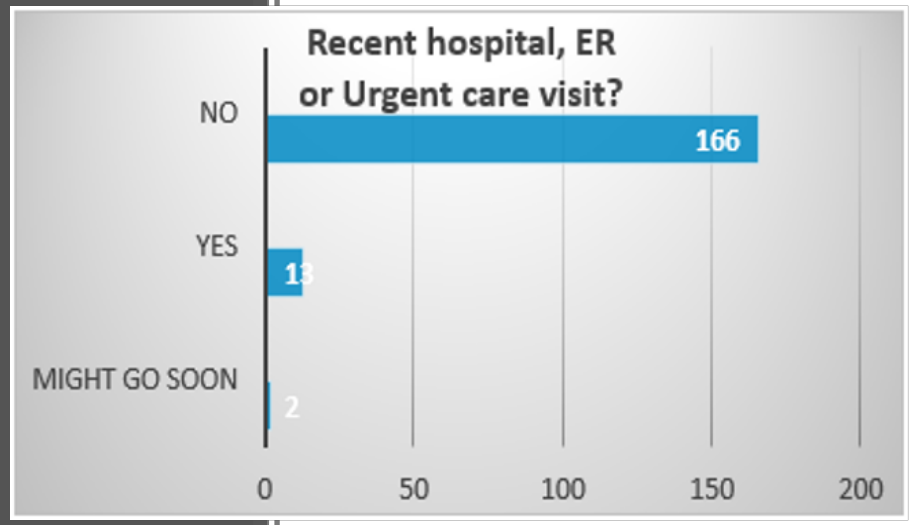
Collecting RWD Daily

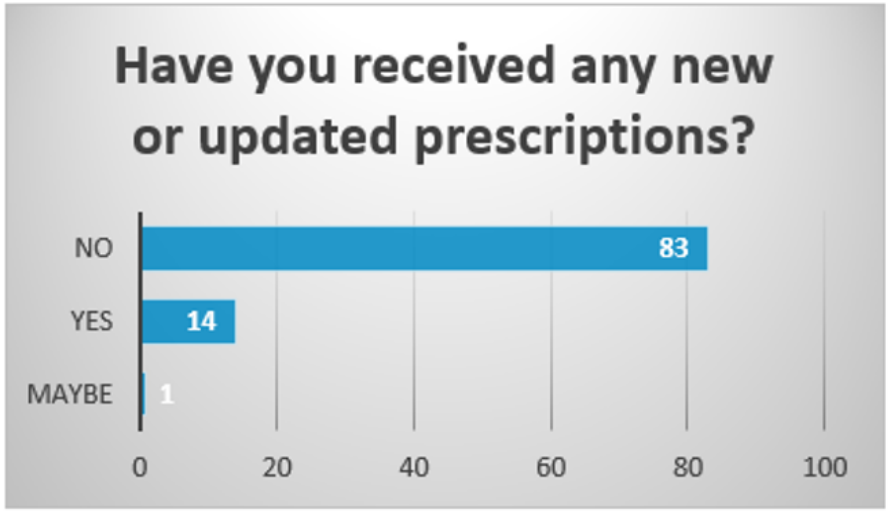


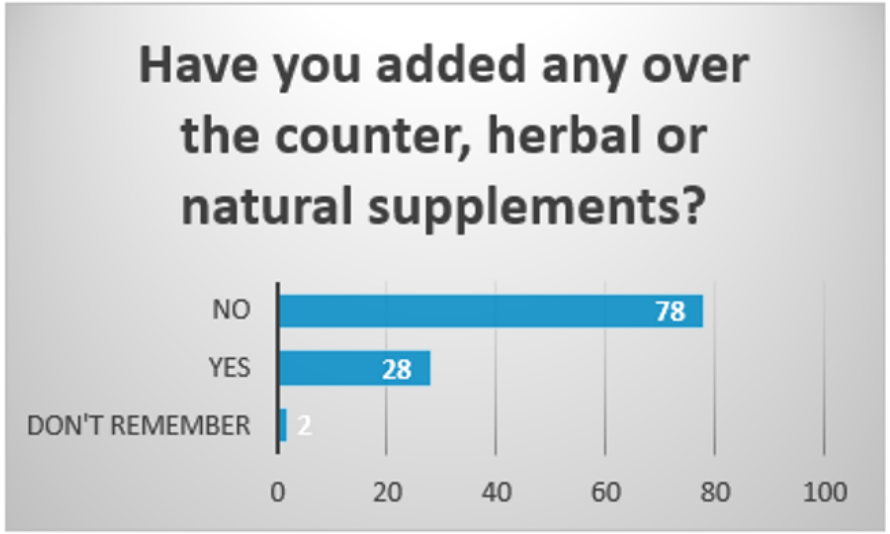
Question Rotation: One question asked during medication dispense

- Any new problems with your health?
- Would you recommend spencer to a friend?
- Are you more active today than yesterday?
- Have you stopped taking any medications?
- Rate your ability to perform activities today
- Have you challenged your brain today?
- How would you rate your overall health today
- How is your emotional health?
- Are you experiencing any pain today?
- How do you feel?
- Will you take all the meds in this dose?
- Are you getting regular care, tests & treatments?
- Any new problems with your health?
- Are you more active today than yesterday?

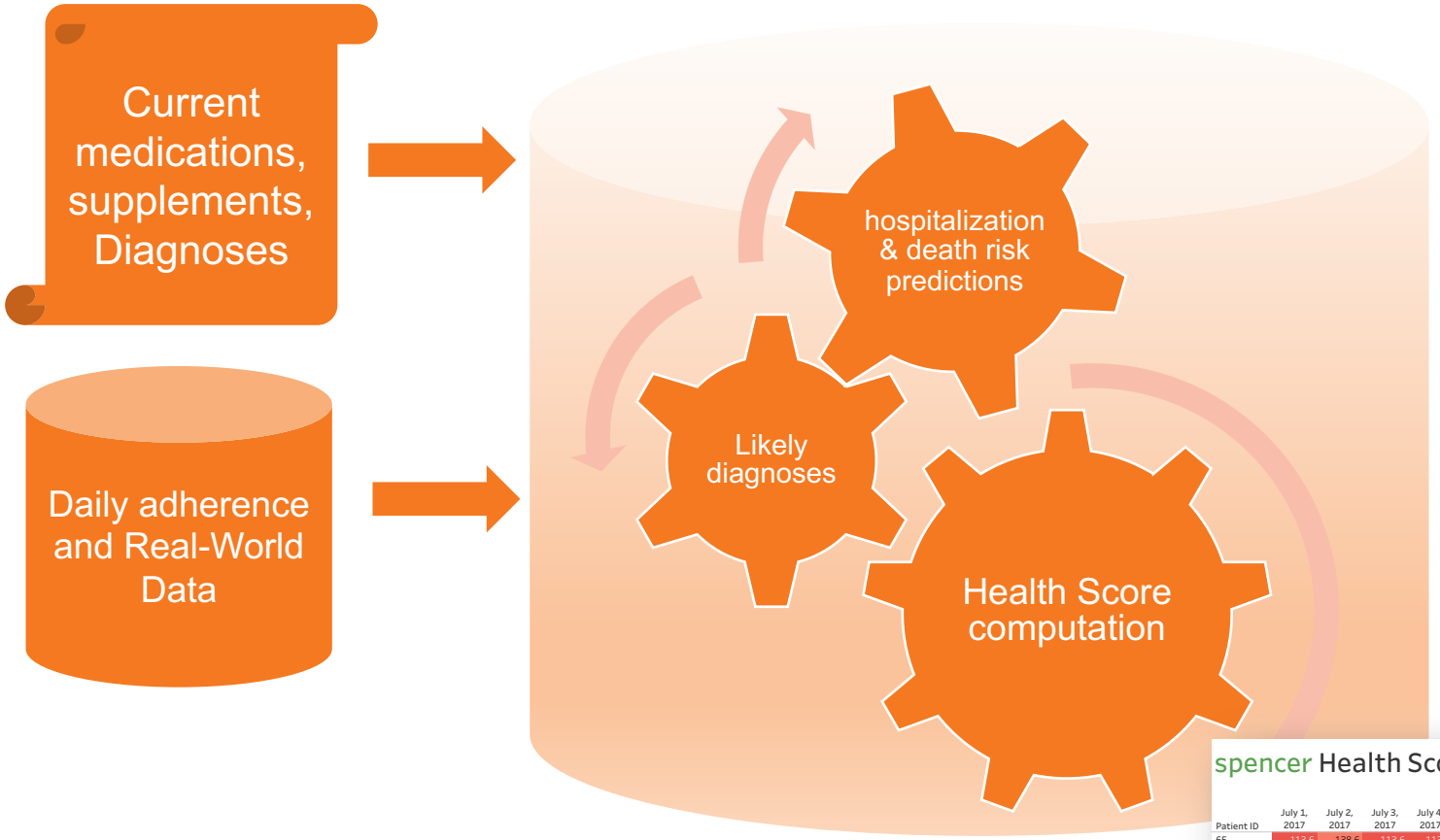
Univariate statistics can give insights into patient compliance and health





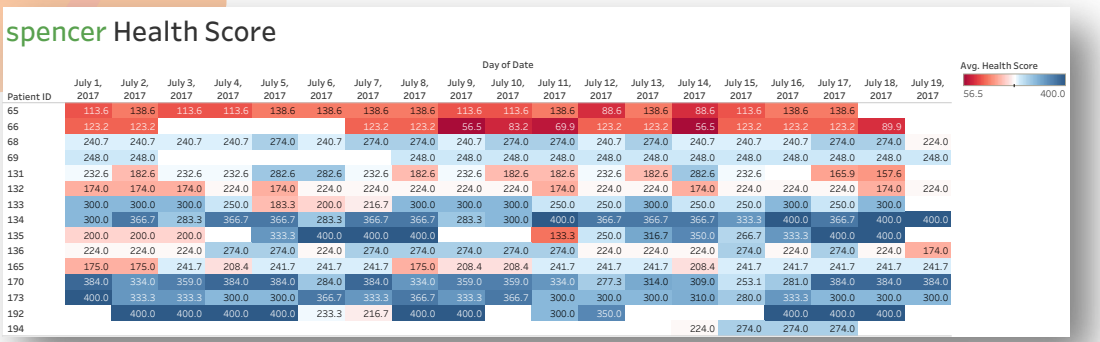


Data can be combined and fed into predictive models



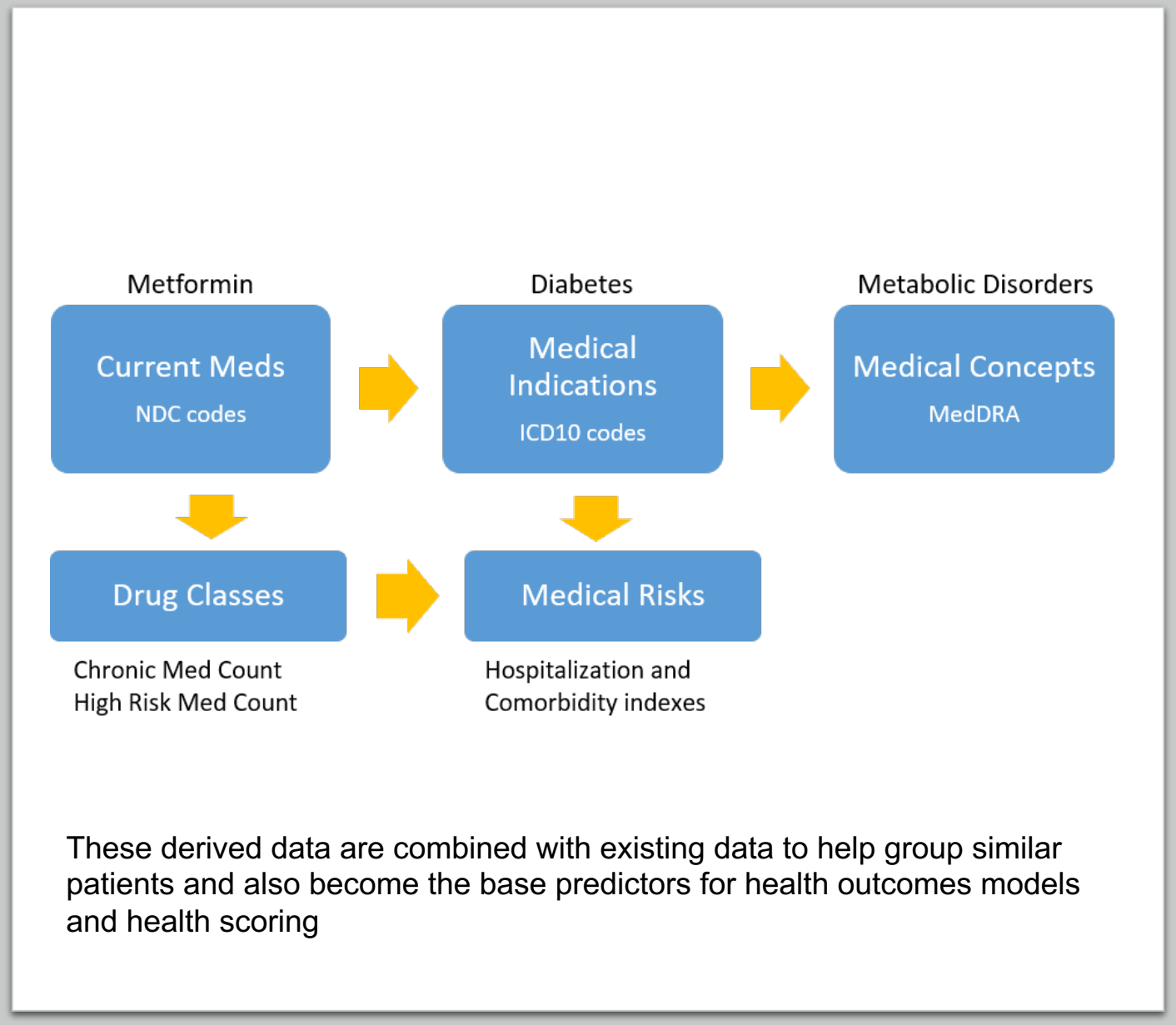
Key inputs

- Drug information
- Daily adherence
- Diagnoses
- Biometric data (e.g. glucose, body weight)
- Health/Disease related questions



Deriving additional data to better understand a cohort of patients

- Clinical Trial participants may or may not provide adequate health history at recruitment
- Current and past medications can be used to potentially fill in gaps
- Ontologies exist for drugs, indications and medical concepts
- Predictive models using ICD10 codes can be used to derive additional data and or reconcile patient records.



These derived data are combined with existing data to help group similar patients and also become the base predictors for health outcomes models and health scoring

Computing Charlson comorbidity and Elixhauser categories from ICD9 codes in R (Medical Risk)

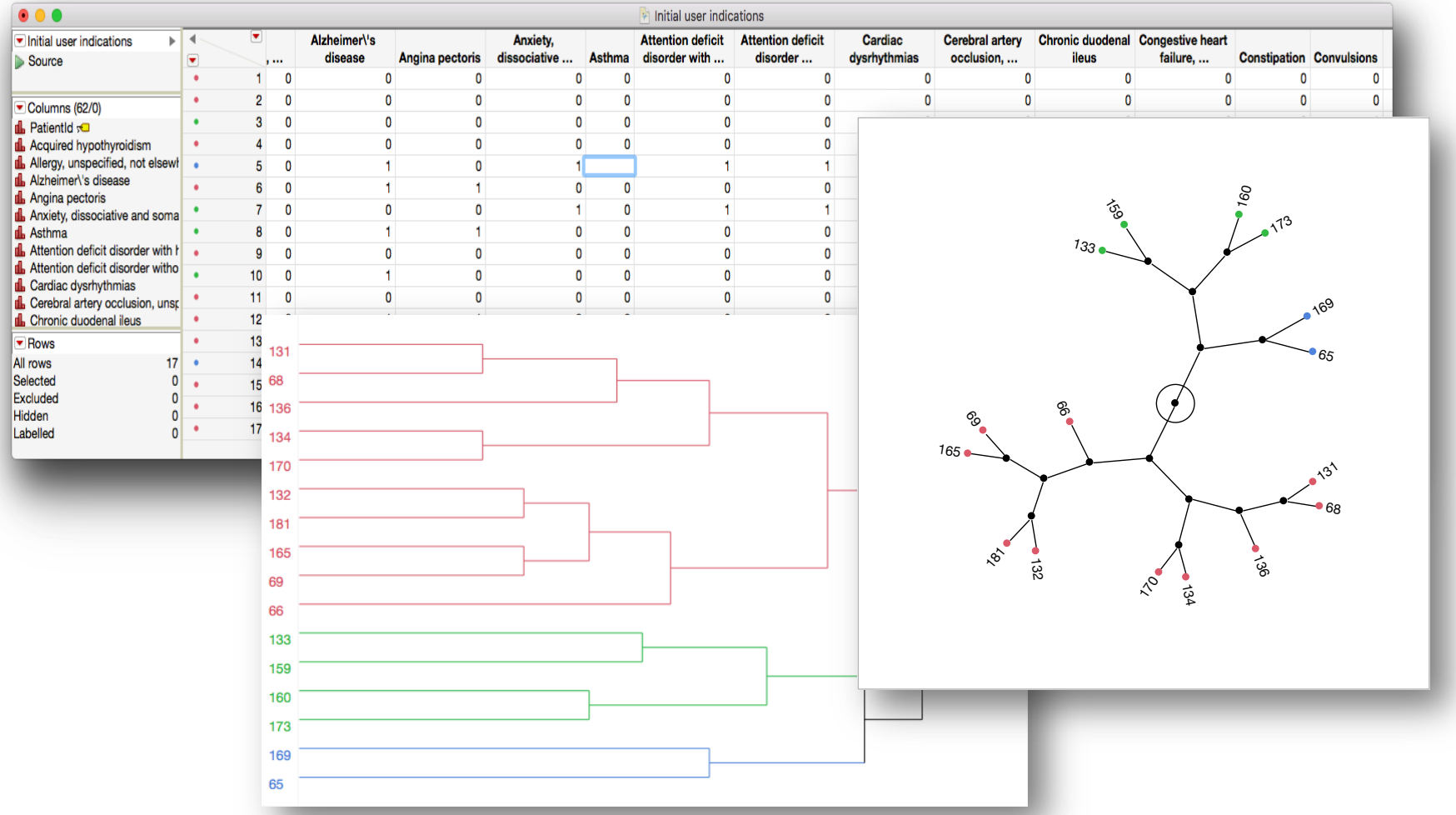
```
# Code for computing comorbidities and risk indexes from icd10m codes

# set up the librarys
library(medicalrisk)
library(plyr)


# pull in my csv file
#first row contains variable names, comma is separator

mydata <- read.table("/Users/codes.dat", header=TRUE, sep=",")

# Now generate a comorbidity dataframe
comord <- generate_comorbidity_df(mydata)

# compute charlson comorbidity indexes for each user
chari <- generate_charlson_index_df(generate_comorbidity_df(mydata))

# compute the Elixhauser Categories
 cases_with_cm <- merge(mydata, icd9cm_elixhauser_ahrq37(levels(mydata$icd9cm)), by.x="icd9cm", by.y="row.names", all.x=TRUE)
# generate crude comorbidity summary for each patient
library(plyr)
hapelix <- ddply(cases_with_cm, .(id),
function(x) { data.frame(lapply(x[,3:ncol(x)], any)) })
# Now Compute RSI (cardiac Risk Stratification Index)
hapddply <- ddply(mydata, .(id), function(x) { icd9cm_sessler_rsi(x$icd9cm) } )

# Now export the results

write.csv(hapddply, file = "/Users//hapddply.csv")
write.csv(chari, file = "/Users/hapcharl.csv")
write.csv(hapelix, file = "/Users/hapelix.csv")
```

Example Output from Medical Risk

id	Num of High Risk Drugs	Charlson index	chf	arrhythmia	valve	pulmcirc	perivasc	htn	htncx	para	neuro	chrnlung	dm	dmcx	hypothy	renlfail	liver
65	0	3	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
66	3	5	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE
67	0	0	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
68	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
69	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
81	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
84	0	0	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
130	0	0	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
131	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
132	3	3	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
133	0	2	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
134	0	0	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
135	0	0	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
136	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
137	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
138	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
142	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
143	1	7	TRUE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
144	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
148	0	2	TRUE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE
149	0	0	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE	FALSE

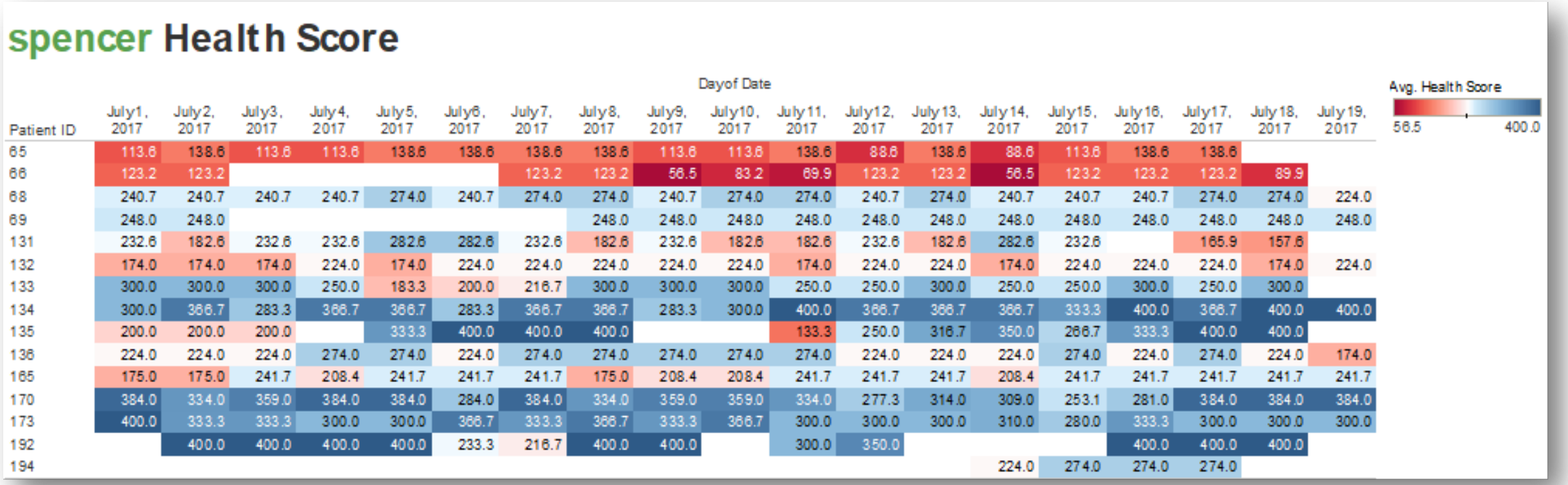
Combined real world data can be used to group similar patients

K-means cluster analysis used to define three distinct groups of patients based on derived medical information



Two users with a similar medical risk profile (eg. diabetes and living alone)

Baseline health information can be combined with real world data collected daily to create a score



Patient ID	July 1, 2017	July 2, 2017	July 3, 2017	July 4, 2017	July 5, 2017	July 6, 2017	July 7, 2017	July 8, 2017	July 9, 2017	July 10, 2017	July 11, 2017	July 12, 2017	July 13, 2017	July 14, 2017	July 15, 2017	July 16, 2017	July 17, 2017	July 18, 2017	July 19, 2017
65	113.6	138.6	113.6	113.6	138.6	138.6	138.6	138.6	113.6	113.6	138.6	88.6	138.6	88.6	113.6	138.6	138.6		
66	123.2	123.2					123.2	123.2	56.5	83.2	69.9	123.2	123.2	56.5	123.2	123.2	123.2	89.9	
68	240.7	240.7	240.7	240.7	274.0	240.7	274.0	274.0	240.7	274.0	274.0	240.7	274.0	240.7	240.7	240.7	274.0	274.0	224.0
69	248.0	248.0						248.0	248.0	248.0	248.0	248.0	248.0	248.0	248.0	248.0	248.0	248.0	248.0
131	232.6	182.6	232.6	232.6	282.6	282.6	232.6	182.6	232.6	182.6	182.6	232.6	182.6	282.6	232.6		165.9	157.6	
132	174.0	174.0	174.0	224.0	174.0	224.0	224.0	224.0	224.0	224.0	174.0	224.0	224.0	174.0	224.0	224.0	224.0	174.0	224.0
133	300.0	300.0	300.0	250.0	183.3	200.0	216.7	300.0	300.0	300.0	250.0	250.0	300.0	250.0	250.0	300.0	250.0	300.0	
134	300.0	366.7	283.3	366.7	366.7	283.3	366.7	366.7	283.3	300.0	400.0	366.7	366.7	366.7	333.3	400.0	366.7	400.0	400.0
135	200.0	200.0	200.0		333.3	400.0	400.0	400.0			133.3	250.0	316.7	350.0	266.7	333.3	400.0	400.0	
136	224.0	224.0	224.0	274.0	274.0	224.0	274.0	274.0	274.0	274.0	274.0	224.0	224.0	224.0	274.0	224.0	274.0	224.0	174.0
165	175.0	175.0	241.7	208.4	241.7	241.7	241.7	175.0	208.4	208.4	241.7	241.7	241.7	208.4	241.7	241.7	241.7	241.7	241.7
170	384.0	334.0	359.0	384.0	384.0	284.0	384.0	334.0	359.0	359.0	334.0	277.3	314.0	309.0	253.1	281.0	384.0	384.0	384.0
173	400.0	333.3	333.3	300.0	300.0	366.7	333.3	366.7	333.3	366.7	300.0	300.0	300.0	310.0	280.0	333.3	300.0	300.0	300.0
192		400.0	400.0	400.0	400.0	233.3	216.7	400.0	400.0		300.0	350.0				400.0	400.0	400.0	
194														224.0	274.0	274.0	274.0		

Summary

- The clinical trial paradigm is evolving
  - The need to establish estimands and conduct sensitivity analyses
  - Real World Data
  - Pragmatic, hybrid and virtual trials
  - Patient Centricity
- Clinical trial simulation is a very useful way to explore different trial designs and quantify the potential impact of multiple factors
- Real world data will become more and more prominent and should be embraced
- Decreasing patient burden will be key to gathering accurate data, increasing adherence and reducing dropouts.

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References

- Guidance for Industry E9 Statistical Principles for Clinical Trials. U.S. Department of Health and Human Ser- vices, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) Geneva: ICH, 1998.
- Appliedclinicaltrialsonline.com/non-adherence-direct-influence-clinical-trial-duration-and-cost
- PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001 Sep 29;358:1033-41.
- Rockhold FW and Ruberg SJ. ICH-E9 reflections and considerations. Pharm Stat 2008; 7(4): 233–235.
- Rockhold FW, Lindblad A, Siegel JP and Molenberghs G. University of Pennsylvania 11th annual conference on statistical issues in clinical trials: Estimands, missing data and sensitivity analysis (morning panel). doi.org/10.1177%2F1740774519853573
- Bonate PL. Clinical Trial Simulation in Drug Development. Pharmaceutical Research 2000; 17(3): 252-256.
- The Coronary Drug Project Research Group. Influence of Adherence to Treatment and Response of Cholesterol on Mortality in the Coronary Drug Project. N Engl J Med 1980; 303:1038-1041