


Simulated Treatment Comparison


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Outline: Simulated Treatment Comparison

- Description of method
- Major analytical steps
- Illustration of the method
- General guidance on application of STC


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Typical Situation

- Pivotal (index) Phase III study have shown that treatment A is efficacious compared to placebo
- Preparing for reimbursement and access submissions
- A competing treatment (B) is already on the market
- Agencies require comparative evidence for A vs. B
- No head-to-head study has been done


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Standard Approach

- Mixed treatment comparison (MTC) or network meta-analysis
 - Gather all studies that include evidence about the efficacy of A and B that could be “linked” through common comparators
 - Extract relative effect estimates of A vs. plc and B vs. plc
 - Perform the MTC to derive summary estimate of A vs. B
- Advantage
 - All available evidence is incorporated in the analysis
 - Uncertainty in study-specific estimates properly taken into account
- Challenge
 - Handling heterogeneity
 - Applicability of findings

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Heterogeneity in MTCs/Meta-analyses

- Are all of the studies measuring the *same* effect?
- Dealing with heterogeneity:
 - Weed out studies that are obviously different, and pool the rest
 - Test for heterogeneity, and if detected, incorporate a random-effect in the estimation of the summary effect
 - Assume variability is completely random
- The question being answered: *What is the average difference between A and B?*
- Does the average difference apply to the index trial?
- *What would the difference have been if B was included in the index trial?*

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Simulated Treatment Comparison

General Idea

- Estimate the expected difference between A and B, had the index study included an arm that was randomized to B
 - Predict key outcomes with treatment B in the index trial (so maintaining population and setting)
 - Derive estimates of comparative metrics (e.g., hazard ratios, odds ratios, mean differences)

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Simulated Treatment Comparison

Main Steps

1. Derive predictive equations for the key outcomes of the index trial of A
2. Calibrate index equations to predict outcomes for B
 - Identify a study of B that is comparable to the index study of A
 - Use data on outcomes with B (ideally patient-level, but more likely published information) to calibrate equations to predict outcomes for B
 - Taking into account differences between the two populations
3. Build a simulation of the index trial based on calibrated equations
 - Generate predictions of outcomes with both treatments
 - Calculate effect measures or other metrics of interest

7 Caro & Ishak (2010), Pharmacoeconomics.

Example

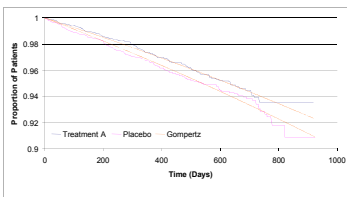
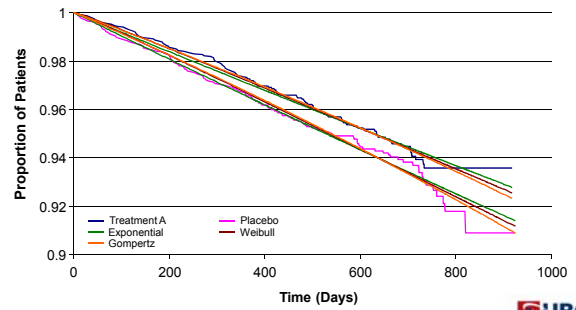
- Index trial compared new treatment (A) to standard care
- Key outcome: Hospitalization
- Want to compare A to leading competitor B
 - Head-to-head study not yet available
- Additional challenge: studies of B have not looked at hospitalization
- BUT, have access to patient level data of an important study of B where hospitalizations were tracked but not fully studied

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Step 1: Derivation of Predictive Equations

- Parametric Survival Analysis
 - Relates risk to determinants
 - Allows prediction of specific event times
- Process
 - Identify best fitting parametric distribution for the data
 - » Test exponential, Weibull, Gompertz, log-normal, log-logistic
 - Identify predictors of risk (among those shown above)
 - » Univariate analysis testing association of each predictor alone
 - Multivariate model with significant predictors from previous step
 - » Trimmed final model including only significant or clinically important predictors in the multivariate model
 - Check model fit against observed data

Derivation of Predictive Equations: Identify Best Fitting Parametric Distribution

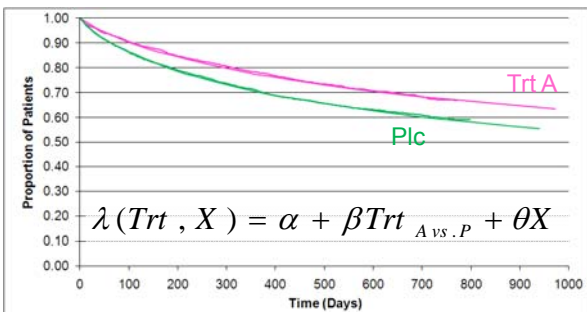


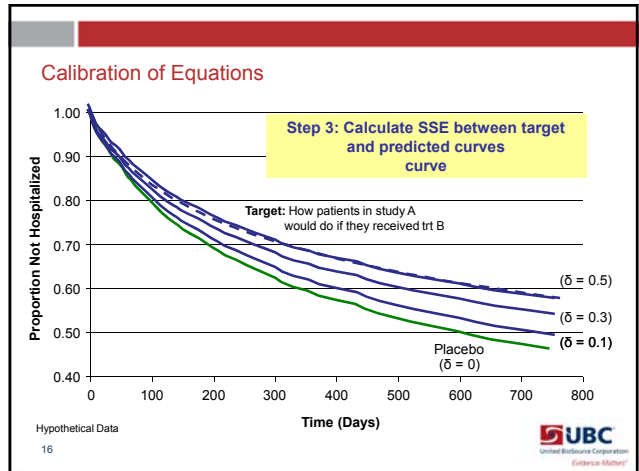
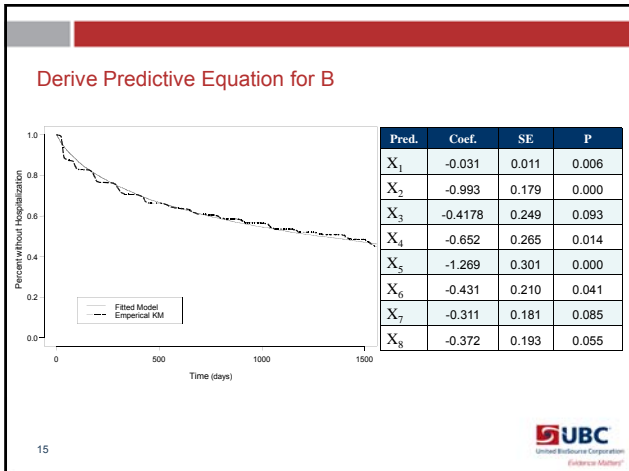
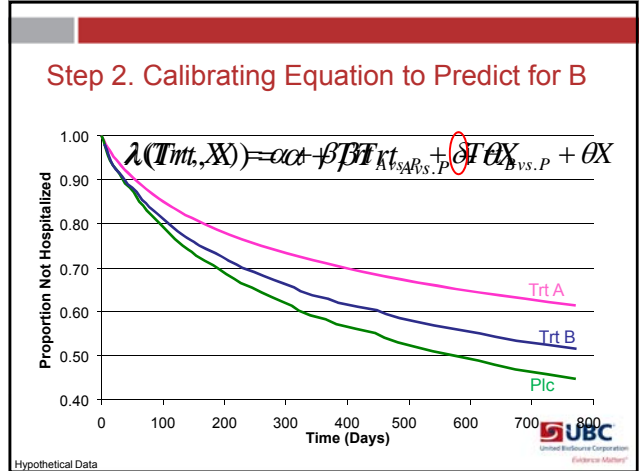
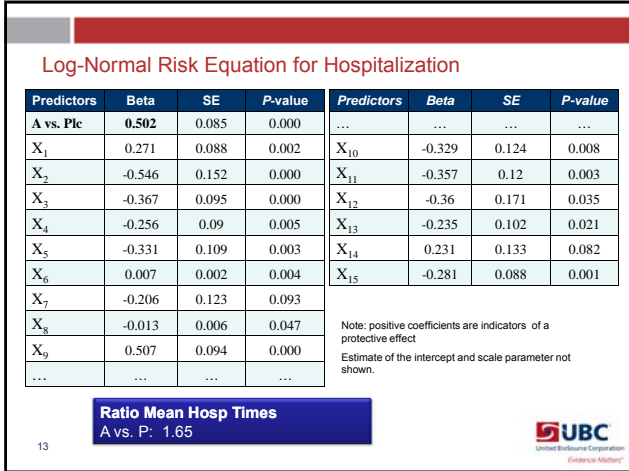
HR for Trt A vs. Placebo
replicated observed result
to two decimals

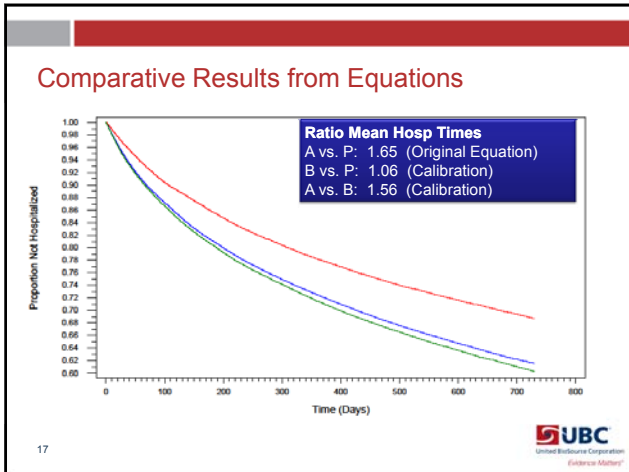
Statistical Criteria for Assessing Model Fit

Model	ll(mult)	ll(model)	df	AIC	BIC
Exponential	-1221.65	-1220.73	2	2445.451	2458.331
Weibull	-1220.97	-1220.05	3	2446.1	2465.42
Gompertz	-1220.84	-1219.92	3	2445.836	2465.156
Gamma	-1220.9	-1219.99	4	2447.985	2473.745
Log-Normal	-1223.62	-1222.39	3	2450.781	2470.101
Log-Logistic	-1221.07	-1220.13	3	2446.257	2465.576

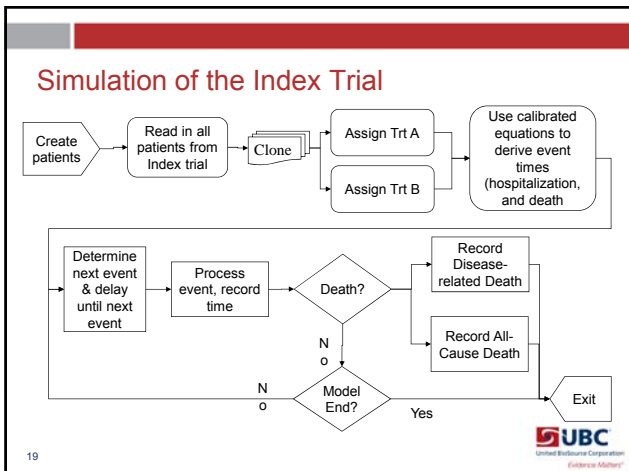
Step 1. Predictive Equation for Time to Hospitalization







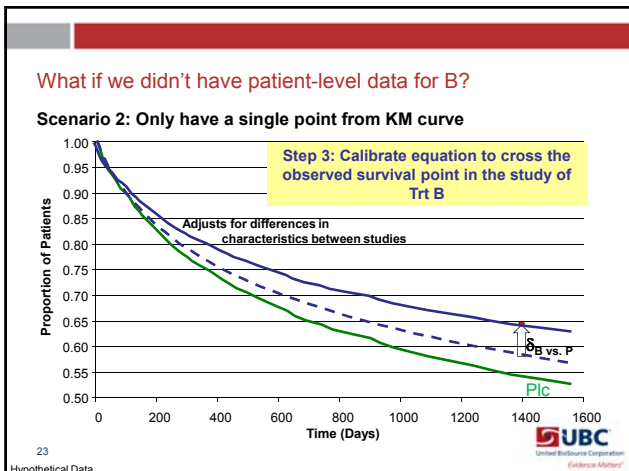
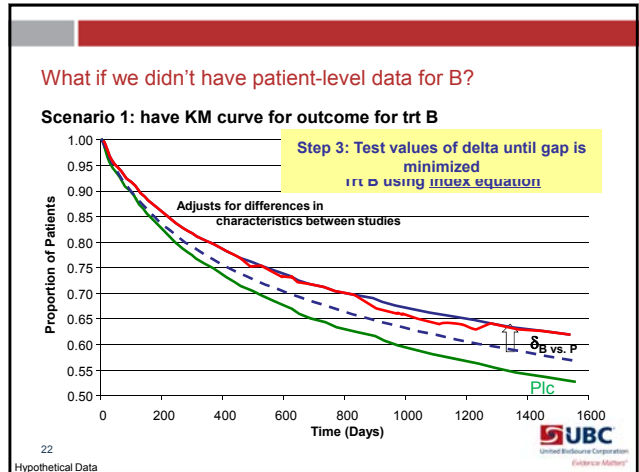
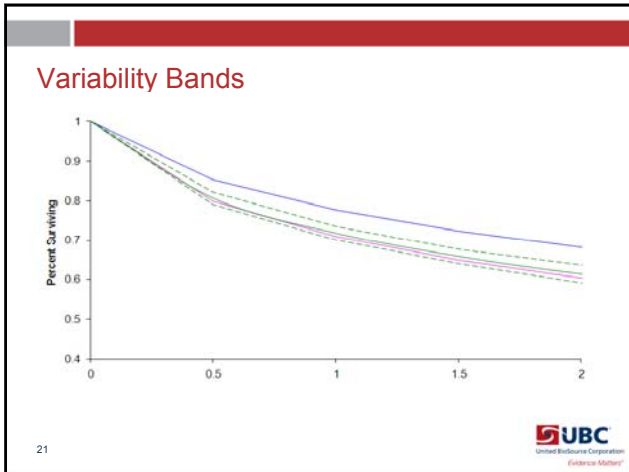
- ### Step 3. Simulation of Index Trial with Added Arm for B
- #### Why Simulate?
- Can replicate original trial, but also modify certain aspects of the study (e.g., patient profile)
 - Used to generate transition probabilities to inform economic modeling
 - Used as a tool to replicate sampling and generate *variability bands* around predicted outcome
 - These are not confidence bands; they do not reflect all sources of uncertainty. Only sampling variability in the conduct of the trial with three arms.
 - Trial simulation framework to help with design of future studies
 - E.g., STC after Phase II to help plan phase III
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Example of Trial Simulation Results

	A from Trial	A Model	P Trial	P Model	B Model
Hosp	29.3%	28.4%	36.9%	35.8%	34.9%
Death from any cause	5.0%	5.0%	6.0%	5.6%	5.3%
Death due to Disease	2.7%	2.6%	3.9%	3.5%	3.3%

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- ### Finding a Comparable Study for Trt B
- What do we mean by “comparable”? How similar do the studies have to be? What differences are important and which are not?
 - Differences in baseline characteristics not a limiting factor. Can handle analytically, but can't rule out confounding from unmeasured characteristics
 - Problematic differences
 - Look for entire subsets are not systematically excluded in one of the studies
 - No extreme difference in FU duration (e.g., 5yr FU in index vs. 6mo FU)
 - Studies with very different treatment protocols
 - Different measurements techniques
- UBC
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Evidence Matters
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Choosing from Multiple Studies for Comparator

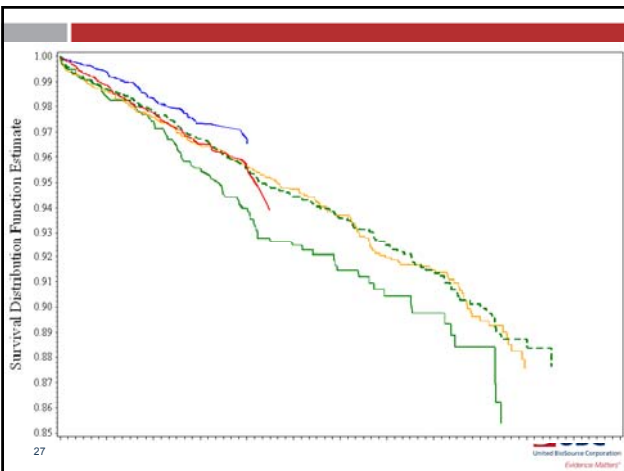
- **What if there are multiple studies for the comparator?**
 - Choose one? Combine? Repeat with each study?
- **Choose one if**
 - Differences between studies point to a closer match to the index trial
- **If no clearly better choice, combining may be a good option**
 - Incorporate all pertinent evidence
 - Combining published data may force some simplification: choosing a specific point on survival curves as a reference value for calibration (as opposed to using the entire curve)
- **Or repeat analyses with each study**
 - To test robustness of results

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Using the Reference Arm of Comparator Studies

- The reference arm of the comparator study can be very useful if the treatment assigned in this group is the same as the reference group in the index trial
- Outcomes in the reference group of the two studies provide a means of checking the comparability of studies
 - Similar outcomes in the two reference arms (after adjusting for population differences) implies comparability of studies
 - Differences (after adjusting for population differences) implies "study effects" that may distort comparative results
 - » May be due to calendar effects
 - » Different outcome definitions
 - » Etc.
 - Can adjust for the study effect in STC result using difference between reference curves

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Uncertainty of the STC Result

- Variability bands shown earlier only reflect sampling variation, not uncertainty
- Uncertainty in the results stems from
 - Uncertainty in the predictions from the predictive equations
 - Uncertainty in the comparator results used for calibration
- Quantifying the uncertainty of the STC result requires propagating the uncertainty in predictions and comparator results through the estimation process
 - The simulation framework allows for this be done very easily
 - This would produce a distribution of results based on which a standard error and confidence interval can be derived

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STC with Other Types of Outcomes

- The example illustrates use of STC with time-to-event outcomes
- The same can be done with continuous (e.g., weight change) or dichotomous (e.g., controlled BP)
- Strategy would be the same, with similar considerations
 - Comparability of studies
 - Criteria for calibration: specific measure (e.g., mean vs. entire curve)
 - Uncertainty of estimates

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Summary

- STC is an alternative approach to deriving indirect comparison
 - Won't always be feasible or appropriate
 - Careful review and comparison of available data sources is an important first step
- STC answers a different question
 - Provides a comparison within the context of a specific study
 - Can be complementary to MTC
 - Differences in results does not imply one or the other is incorrect
- Work is ongoing to develop and refine the approach through applications

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