Trial Simulation Modeling in the Era of Comparative Effectiveness Research

David Thompson, PhD
Senior Vice President
OptumInsight (formerly i3 Innovus)
Boston, USA

Contact:

david.thompson@innovus.com

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Topics

- Describe how CER trials differ from traditional registration trials
- Introduce trial simulation modeling and show why it's more complicated to perform for CER trials
- Demonstrate how to perform trial simulation modeling in context of CER
- Provide case study example to illustrate use of trial simulation model for refinement of study protocol

Trial Simulation Modeling: The Basics

- What is it?
  - Development of model based on planned trial design to assist in predicting expected trial outcomes, assessing modifications to study design, etc
- Why do it?
  - Because clinical trials can be costly & risky
  - Modeling can leverage existing information to help refine study design to improve efficiency of trial implementation, reduce risk of bad trial outcome
- How to do it?
  - Several modeling techniques can be used, but patient-level simulation best reflects the context of a trial

Comparative Effectiveness Research: Implications for Trial Design

Characteristic	Registration Trials	CER Trials
Setting	Experimental	Real-world
Patients	Selected to gain insight on pure treatment effect	Selected to gain insight on real-world treatment effects
Comparator(s)	Usually placebo (if active-control then non-inferiority design)	Active, including non-drug interventions
Measure(s)	“Efficacy”, primarily relevant to investigators & pharmacologists	“Effectiveness”, primarily relevant to patients, providers & payers
Blinding	Always (unless infeasible)	Not always
Follow-up	Usually long enough only to assess intermediate endpoints	Usually long enough to capture full episode of care
Analyses	Usually averaged over all patients, with statistical control of hetero-geneity of response	Usually conducted overall & for relevant patient subgroups to assess heterogeneity of response

Trial Simulation Modeling in CER: Key Elements

- Prediction equations
- Identifying & handling uncertainty
- Assessing predicted trial outcomes
- Use of model to inform modifications/refinements to CER trial design

Trial Simulation Modeling in CER: Prediction Equations

- As with any model, an analytic framework to link inputs to outputs is needed
- In trial simulation modeling, equations that predict patient-level trial results from patient characteristics (demographic & clinical) and treatment assignment are key
- Estimation of the prediction equations can be done based on:
  - Patient-level data from prior trials
  - Observational data (eg, registries, database analyses)
  - Rigorous analysis of published data (eg, network meta-analysis)

Trial Simulation Modeling in CER: Handling Uncertainty

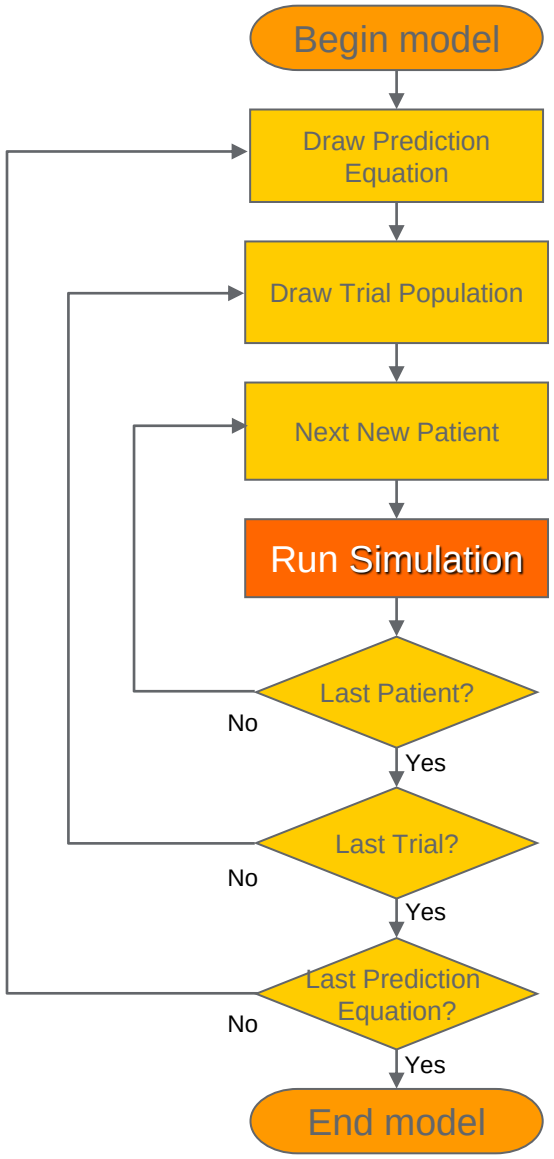
- Clinical trials are subject to two major sources of uncertainty:
  - Between-patient heterogeneity of patient characteristics during sample selection process
  - Within-patient randomness in treatment response

- Trial simulation models are subject to another source of uncertainty:
  - In relationships between patient characteristics, treatment assignment, and treatment outcome (ie, in the prediction equations)

- Trial simulation model needs to account for all three sources of uncertainty; How?
  - ➢ Multi-level, nested Monte Carlo simulation

Trial Simulation Modeling in CER: Multi-Level Monte Carlo Simulation

- Simulation involves three distinct processes:
  1. Drawing of alternative prediction equations
     - Do this R times
     - Captures prediction equation uncertainty
  2. Simulation of trials within a given prediction equation:
     - Do this T times
     - Captures uncertainty about composition of trial sample deriving from heterogeneity in population
  3. Simulation of individual patients within a given trial:
     - Do this P times
     - Captures uncertainty deriving from within-patient randomness in treatment response



- Each model simulation therefore involves R·T·P individual patient simulations

Trial Simulation Modeling in CER: Assessing Predicted Trial Outcomes

- For each of the R·T trials in any given simulation, the model should:
  - Predict study measures by treatment group
  - Compute p-values for the predicted treatment group differences

- These computations can then be used to estimate likelihood of various trial outcomes; eg, a given treatment group will be favored:
  - Can include a statistical significance threshold (eg, p<.05) and/or
  - Can include effect size threshold to predict clinically significant difference

- Facility to assess predicted trial outcomes in user-defined subgroups also key for CER trials

Trial Simulation Modeling in CER: Illustrative Example

- Phase IV CER trial planned for inpatient treatment of skin infections in the United States

- Key elements of planned trial design:
  - Head-to-head comparisons of two antibiotics (Drug A vs Drug B)
  - Primary study measure is hospital length of stay (LOS)
  - Patients required to be hospitalized for the infection, but other elements of inclusion/exclusion criteria open for consideration:
    - » Patient demographics (age, sex, race)
    - » Type & severity of infection
    - » Comorbidity status

Illustrative Example: Specification of Prediction Equations

- Model prediction equations express LOS as a function of
  - Demographics (age, sex, race)
  - Infection type (wound, abscess, diabetic ulcer, non-diabetic ulcer, other)
  - Infection severity (mild/moderate, severe)
  - Comorbidities (BMI, history of vascular disease, history of diabetes)

- Separate regression equations were specified for Drug A and Drug B so as to capture all treatment-by-factor interaction effects

Illustrative Example: Estimation of Prediction Equations

- Prediction equations estimated using patient-level data from multi-national phase III trial:
  - Head-to-head comparisons of Drug A vs B
  - Cure was primary study measure; LOS was a secondary measure
- Accelerated failure time analysis was used to estimate the prediction equations, assuming a Weibull distribution for the error term
- A total of R=1,000 prediction equations were estimated, using bootstrapping (with replacement) of the overall trial population (n=595)

Illustrative Example: Model Outputs & Analyses

- Key model outputs include:
  - Predicted mean LOS for Drugs A & B and predicted mean difference in LOS between treatments
  - Likelihood that predicted mean difference in LOS would favor Drug A or Drug B at p-values of <.01 & <.05

- Key model outputs presented:
  - Over all trial patients
  - User-defined subgroups

- Model also incorporates sensitivity analysis module to identify potential patient inclusion/exclusion criteria that would impact trial results

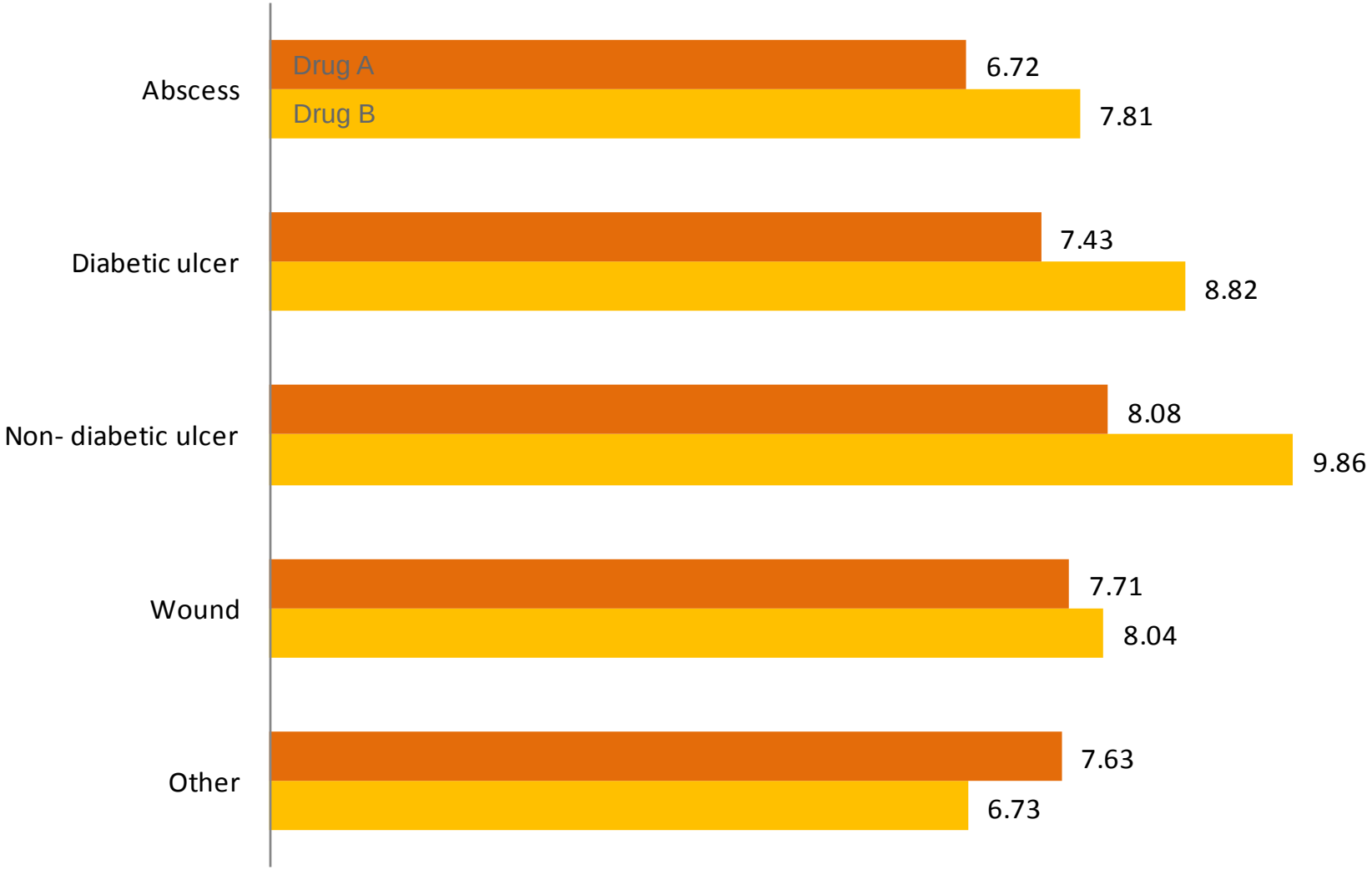
Illustrative Example: Predicted Hospital LOS (days)

P(A > B) in trial:
69% at p<0.01
83% at p<0.05

P(B > A) in trial:
0% at p<0.01
0% at p<0.05

- Note that P(A > B) is conceptually similar to statistical power, but model incorporates uncertainty in both effect size & standard deviation, which are usually assumed to be known & fixed in traditional power calculations

Illustrative Example: Subgroup Analysis of Predicted LOS (days)



Illustrative Example: Rank-Ordering of Most Impactful Exclusion Criteria

Patient Characteristic	Subgroup excluded	Drug A	Drug B	DIff (B-A)	P(A > B) at p<0.01	P(A > B) at p<0.05	% of patient population remaining
Primary Diagnosis	Wound	7.29	8.42	1.14	0.948	0.981	56.3%
Vascular Disease History	No	8.26	9.30	1.04	0.679	0.756	20.3%
Severity	Severe	7.12	8.04	0.92	0.822	0.901	42.8%
Gender	Male	7.40	8.32	0.91	0.807	0.892	45.8%
Primary Diagnosis	Other	7.49	8.36	0.87	0.817	0.915	93.3%
BMI	Overweight	7.40	8.27	0.87	0.806	0.905	75.4%
Race	White	7.00	7.82	0.82	0.817	0.913	44.6%
Diabetes History	Yes	7.28	8.09	0.81	0.760	0.873	68.6%
Age	65 plus	7.24	8.02	0.78	0.777	0.887	75.8%
BMI	Obese	7.49	8.26	0.76	0.705	0.839	68.9%
Race	Black	7.70	8.46	0.76	0.651	0.786	71.2%
Age	31 to 64	7.71	8.47	0.76	0.593	0.706	38.2%
Race	Asian	7.50	8.25	0.75	0.698	0.845	99.3%
[illegible]	18 to 30	7.61	[illegible]	[illegible]	0.652	0.[illegible]	[illegible]
[illegible]	Other	7.57	[illegible]	[illegible]	.632	0.	[illegible]
[illegible]	Yes	7.29	7.98	0.69	0.671	0.	[illegible]
Primary Diagnosis	Diabetic ulcer	7.50	8.17	0.67	0.590	0.747	88.4%
Diabetes History	No	7.95	8.59	0.64	0.526	0.645	31.4%
Severity	Non-severe	7.77	8.40	0.63	0.520	0.671	57.2%
Gender	Female	7.56	8.19	0.63	0.545	0.695	54.2%
Primary Diagnosis	Abscess	7.75	8.37	0.62	0.478	0.630	74.8%
Primary Diagnosis	Non-diabetic ulcer	7.40	7.99	0.59	0.563	0.730	87.2%
BMI	Normal	7.61	8.20	0.59	0.478	0.623	55.7%

Excluding patients with wounds would increase the predicted difference in LOS …

as well as the likelihood of a positive trial outcome for Drug A

But would severely limit numbers of patients eligible for enrollment in the study

Illustrative Example: How the Model was Used

- Model sparked heated debate over refinement of study inclusion/ exclusion criteria

- As relates to primary diagnosis:
  - Model results suggest trial would have greater likelihood of success if wounds & other infections were excluded
  - However, these constitute about one-half of all patients hospitalized for skin infections, so concerns about slow enrollment and pigeon-holing of treatment were expressed

- As relates to other patient characteristics:
  - It was recognized that several factors (eg, BMI, history of vascular disease, age) could be correlated with diabetes
  - Study sponsor concerned about limiting study to diabetic population

Trial Simulation Modeling in CER: Limitations

- As with all modeling efforts, model outputs are only as reliable as the model inputs … and data limitations can be significant in CER
- Although multi-level Monte Carlo simulation permits handling of some key sources of uncertainty, others may remain (eg, omitted variables in prediction equations)
- Single-variable sensitivity analyses assist in refining patient inclusion/ exclusion criteria, but ignore intercorrelations between variables

Trial Simulation Modeling in CER: Conclusions

- Interest in CER has revitalized a range of methodologic approaches for comparative analysis of medical interventions, including phase IV trials
- Trial simulation modeling has long been a valuable tool for trial planning, but is more complicated to perform for CER trials
- Despite its limitations, trial simulation modeling can help improve the design of CER trials for optimum usefulness of study results

Muito Obrigado!
Thank You!

david.thompson@innovus.com

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