# Virtual Population Simulation as a Source of Expected Event Rates

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Estimating the number of patients needed for a clinical study (i.e., sample size estimation) is critical to formulating a statistically robust trial design that avoids generating inconclusive results. The literature contains several examples of trials that failed to generate conclusive results due to insufficient sample size, with reasons varying from poor sample size estimation, poor enrollment or patient dropout.[1,2] Sample size also has major implications on the cost and timing of a clinical trial.

A key determinant to sample size estimation is the expected rate of events in the trial population. Uncertainty about expected rates in the target population poses a challenge for estimating sample size. While clinical trialists can use observed rates drawn from prior relevant studies or risk engines to inform expected rates, such as those for cardiovascular events (e.g., Framingham, ARIC, Dundee, SCORE), these sources can vary substantially in their estimates. Additionally, comparing results across these sources is difficult because the source populations on which they are based can vary by demographic characteristics, geography, healthcare system, clinical history, and severity of disease. For instance, the frequently used Framingham Risk Score, which estimates the 10-year risk of developing coronary heart disease and is useful in informing physicians and patients about cardiovascular risk, has become outdated over time as clinical guidelines and healthcare practice patterns have changed.

Virtual population simulation can help overcome some of these limitations. Simulation allows one to play out the lives of thousands of virtual patients as they accumulate disease burden; to include current and evolving clinical practice; and to forecast the expected rate and pattern of event rates over several years (e.g., myocardial infarction [MI], major adverse cardiac events [MACE], renal progression) for a given population. A theoretically unlimited number of scenarios with different populations, treatment guidelines, and patient behaviors (e.g., medication non-compliance) can be run simultaneously — with results available today. The use of virtual population simulation allows researchers to examine how inclusion/exclusion criteria affect the characteristics of the baseline population and the size of the eligible population.

## CASE STUDY: FORECASTING MACE RATES FOR PLANNING A CARDIOVASCULAR (CV) OUTCOMES TRIAL

The anti-obesity space has historically been a "Bermuda Triangle" filled with failed or withdrawn drug candidates. One drug was withdrawn from the market due to heart valve damage; another was withdrawn due to CV risk; and yet another did not receive U.S. Food and Drug Administration (FDA) approval due to suicide risk. However, recently there have been successes. Two drugs were approved in 2013 but only after overcoming birth defect and cancer risk issues, respectively.

A biopharmaceutical company is developing a drug for obesity and weight management which is a combination of two approved and marketed drugs, one used for smoking cessation and the other for alcohol dependence. Based on trial data showing weight loss with the new drug, an FDA advisory committee recommended approval with a **post-approval** commitment to study CV safety risks. However, in early 2011, the FDA issued a Complete Response Letter stipulating the need for a **pre-approval** CV outcomes trial as well.

After some negotiation, the company and the FDA eventually arrived at a "reasonable and feasible" path forward that could enable resubmission of the New Drug Application (NDA). The FDA had several stipulations on trial design, including:

- Background rate of 1.0–1.5% risk of major CV event (annual)
- 95% confidence interval (CI) to exclude a hazard ratio (HR) of 2.0 and 1.4 at interim analysis and final analysis

As a result, a trial design was needed that was acceptable to the FDA and resource-efficient with sufficient MACE events, optimal study enrollment and duration, and clear interpretation. For background CV event rate determination, the company used

Phase 3 data and published CV risk engines to estimate 10-year risk.[3] While results were encouraging, the risk engines had limitations, including:

- Lack of consistent patient population across engines
- Current standard of care not uniformly implemented across engines
- Inconsistent endpoints available across engines (e.g., MI not available in all engines)

A decision was made to pursue simulation, specifically the exploration of the contributions of different inclusion/exclusion (I/E) criteria to MACE event rates. Several population subgroups were identified based on variations of I/E criteria, e.g., High-risk CV with:

- Age >50, BMI >27
- Age >50, BMI >30
- Age >50, BMI >30 + HTN (hypertension)
- Age >50, BMI >30 + HTN + DM (diabetes mellitus)

Combinations were also based on: age, sex, body mass index (BMI), weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG), HbA1c, high-density lipoprotein (HDL), low-density lipoprotein (LDL), smoking status, and other parameters.

Patients were then drawn at random from the virtual population, and those virtual patients meeting I/E criteria variations were recruited into the simulation. Event rates (MACE and MACE components — MI, stroke, cardiovascular disease [CVD] death) were estimated annually for each I/E criteria scenario over a 10-year period. Projected MACE rates of I/E criteria variations enabled the company to understand expected rates and to sculpt the trial population.

The simulation data were shared with the FDA after the Complete Response Letter was received and during negotiations with the FDA on securing clearance for its CV study protocol. In February 2012, the FDA cleared the company's study protocol.

In conclusion, which methods or tools will work best to address specific study needs depends on the availability and reliability of expected event rate data and applicability of risk scores to the population of interest. The clinical trialist now has more options, however, to generate or refine estimations — including virtual population simulation.

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*References*

[1] Brancati F, *et al.* Midcourse Correction to a Clinical Trial When the Event Rate is Underestimated: the Look AHEAD (Action for Health in Diabetes) Study. *Clin Trials.* 2012; 9(1):113–124.

[2] Cowan CC, *et al.* A Randomised Double-blind Placebo-controlled Trial to Determine the Effect of Cranberry Juice on Decreasing the Incidence of Urinary Symptoms and Urinary Tract Infections in Patients Undergoing Radiotherapy for Cancer of the Bladder or Cervix. *Clin Oncol (R Coll Radiol).* 2012 Mar; 24(2):e31–e38.

[3] Chilton R, Buse J, Plutzky J, Wang W, Strack T, Clapper B, Harris-Collazo R, Klassen P. Naltrexone SR/Bupropion SR Combination Therapy Improves Predicted 10-Year Risk of Cardiovascular Disease, Coronary Heart Disease, Myocardial Infarction, and Congestive Heart Failure. The Obesity Society Annual Scientific Meeting; 2011 Oct 1–5; Orlando, FL.

[4] Yang F, Ye J, Pomerantz K, Steward M. Potential Modification of the UKPDS Risk Engine and Evaluation of Macrovascular Event Rates in Controlled Clinical Trials. *Diabetes Metab Syndr Obes.* 2013 Jul 12; 6:247–256.

*Additional sources*

Analyst reports, company press releases