Expansion of Expected Net Present Value Framework for Evaluating Patient Engagement Methods

CLINICAL TRIALS TRANSFORMATION INITIATIVE

I. INTRODUCTION

The value of patient engagement is increasingly recognized as an important aspect of clinical trials – one that has the potential to shorten development times and increase technical and regulatory success rates. This resource bridges that trend with the common use of customized expected net present value (eNPV) models by pharmaceutical and biotechnology companies to support financial and resource allocation decision making. The primary aim of this resource is to expand on CTTI's initial eNPV modeling and assist researchers and companies in constructing models for a wide variety of scenarios (i.e., other disease categories, additional patient engagement methods).

Building on a study conducted by the Clinical Trials Transformation Initiative (CTTI), which demonstrated substantial returns to investments when engaging patients in trials **[Levitan et al., 2018]**, this report, created by Tufts and well-received by the clinical trials enterprise, outlines recommendations for variables to input into eNPV models so that individual companies can perform their own return on patient engagement assessments.

Additionally, an addendum (see pages 5-12) is included with an expanded list of variables and references to guide more robust and expansive eNPV modeling activity. This includes:

- Inputs associated with different therapeutic classes and specific patient-centric initiatives (e.g., advocacy group collaborations; patient advisory boards; participation convenience enhancements; and the return of plain language clinical trial results)
- An eNPV model of the profitability of applying various patient engagement methods in the clinical trial process
- Potential data sources that may be used to parameterize the model

II. ECONOMIC MODEL DEVELOPMENT AND MARKET PARAMETERS

Net present value (NPV) means the after-tax real (inflation-adjusted) present value of future net cash flows. eNPV is the risk-adjusted NPV, which accounts for the fact that not all drug development projects will succeed in the sense of proceeding through all development phases to regulatory marketing approval and market launch. The eNPV model for a base case scenario requires estimates and assumptions for a number of elements of the development and commercialization of a new drug or a line extension (LE) to an already-approved drug. For ease of exposition we refer to new drugs and biologics as new molecular entities (NMEs).

The key parameter categories and variables are the following:

- **Development Costs for NMEs and LEs**
  - Clinical trial out-of-pocket (resource) costs for an indication by clinical phase by therapeutic class or molecule type
  - Development and regulatory out-of-pocket costs incurred during the regulatory review period by therapeutic class or molecule type
- **Development and Regulatory Approval Time**
  - Duration of clinical testing by clinical phase by therapeutic class or molecule type
  - Duration of the regulatory review period (time from submission of an application for marketing approval to approval of the application) by therapeutic class or molecule type

- **Individual Clinical Trial Performance and Quality by Clinical Phase and Therapeutic Class**
  - Ethical review and approval of the protocol
  - Study start-up and initiation timelines
  - Screening, recruitment, and retention rates
  - Study close-out timelines

- **Development Risk for NMEs and LEs**
  - Estimates of clinical phase transition rates (likelihood that a new drug will proceed in development from one clinical phase to the next) by therapeutic class or molecule type
  - Estimate of the probability of regulatory approval for a new drug by therapeutic class or molecule type

- **Sales and Marketing Expenses**
  - Pre-launch period (assumed to be one year), launch year, and immediate post-launch period (assumed to be the first three years after the launch year) sales and marketing expenses (assumed to be a percentage of peak-year sales)
  - Sales and marketing annual expenses prior to loss of patent protection (assumed to be a percentage of peak-year sales)

- **Other Costs**
  - Annual cost of goods sold (assumed to be a percentage of revenues)
  - Other operating expenses (assumed to be a percentage of revenues)
  - Medical affairs expenses (assumed to be a percentage of revenues)
  - Working capital accounts receivable days (assumed)
  - Working capital inventory days (assumed)

- **Pharmaceutical Industry System Parameters**
  - Effective corporate net income tax rate
  - Cost of capital for pharmaceutical firms (discount rate for future costs and revenues)
  - Effective patent life (time from launch to loss of patent protection; may vary by therapeutic class given differential development times)

- **Revenues for NMEs and LEs**
  - Peak-year sales by therapeutic class
  - Annual net sales (gross sales minus discounts and rebates) by therapeutic class (based on peak-year sales and an assumed sales growth curve)
  - Net sales erosion rates after generic entry by therapeutic class and molecule type

Parameter values based on assumed values are judgment calls drawn from experience. The impacts that these assumed values have on results can be scrutinized closely through extensive sensitivity analyses based on a wide range of reasonable variation in base case numbers. Other parameter values can be estimated but can also be subjected to sensitivity analysis (with variation in some cases determined by variation ascertained by examining the data or variability information in published estimates).

III. PUBLIC AND PATIENT ATTITUDES AND EXPERIENCES IN CLINICAL TRIALS

Assessments of public and patient attitudes and experiences provide insight into factors — across all stages of clinical trial participation—that most contribute to study volunteer recruitment and retention rates. The impact of patient-centric approaches can be weighted based on the perceived importance of various factors by the population/subpopulation that they target. These factors include:

- Understanding of the clinical research process
- Awareness of and confidence finding clinical trials
- Perceptions of the risk and benefits of participation
- Willingness to participate
- Stakeholders (e.g., physicians, nurses) that are expected to play a role in facilitating participation
- Preferences associated with convenience and ease of participation
- Concerns about privacy and confidentiality
- Preferences associated with disclosure and transparency

IV. PATIENT-CENTRIC APPROACHES TO INCREASE STUDY VOLUNTEER ENGAGEMENT

During the past 7–10 years, pharmaceutical, biotechnology, and contract service provider companies have implemented a wide range of patient-centric approaches to simplify and improve the feasibility and relevance of study protocols; increase the convenience of participation; and to build trust and reinforce collaboration and commitment.

Based on research published in the literature, the following approaches have been used the most extensively to date (and, as a result, where impact data are available) by sponsors and CROs:

- Advocacy group collaborations
- Patient advisory boards
- Wearable devices and mobile applications
- Social and digital media communication platforms
- Home nursing networks and telemedicine
- Electronic informed consent
- The return of plain language clinical trial results

Primary impact measures that have been characterized anecdotally, and in some cases quantified, for individual case studies include:

- Overall clinical trial cycle time
- Recruitment rates
- Retention rates
- Reduction in the number of protocol procedures
- Change in the number and location of investigative sites
- Prevention and reduction in the number of protocol amendments

NOTABLE REPORTED IMPACT AREAS

Advocacy Group Collaboration	Advisory Boards/Panels to Inform Protocol Design, Study Feasibility
• IRB review and approval cycle: 1 month • Study planning cycle time: 3 months • Patient enrollment cycle time: 20%–30% reduction in overall cycle time • Increase in patient participation rates: 15%–20%	• On average, 1.3 visits removed from the protocol schedule • On average, 1.5 procedures removed from the protocol • 3.8 changes made to the language in the informed consent form • 7 changes to study positioning and communication material • On average, added 3 months of additional time to the clinical trial planning process
Solutions Improving Participation Convenience	**Plain Language Clinical Trial Results**
• Increased interest/willingness to participate resulting in higher recruitment rates • Increased patient satisfaction levels resulting in higher retention rates • Improved retention rates by 30%–40% • Reduced study timeline 20%-35% • Telemedicine trials reduced typical clinical trial costs by 30%	• Improved recruitment rates by 15%–20% • Improved retention rates by 40%–50% • Contributed to significantly higher levels of overall participation satisfaction

V. EXAMPLES OF ANALYSES THAT CAN BE PERFORMED

There are a number of analyses that can be performed including baseline assessments and sensitivity analyses. We suggest establishing metrics for components of an NPV analysis relevant to a traditional drug development paradigm. This will result in deriving an NPV and an eNPV for what will constitute the base case that can be compared to output from other analyses.

Separate base cases can be derived depending on therapeutic class and molecule type. Changes in NPV and eNPV from implementing various patient engagement activities can be measured against these base cases.

The robustness of the results can be tested through various sensitivity analyses. Not every parameter in the model can be expected to have substantial uncertainty or variability regarding its value, and so it can safely be taken to be constant. Others can be varied in one of two ways: (1) If no information on the distribution of values for a parameter is available, then low and high values for the parameter can be determined based on a percentage of the base case value (e.g., +/- 20% of the base case value); (2) Alternatively, if something is known about the distribution of potential values, then measures of distribution variability can be used to determine the sensitivity upper and lower bounds. For example, if the mean and standard deviation have been estimated for a parameter, then +/- one or two standard deviations above and below the mean can be used to determine the sensitivity range.

The analysis can also go beyond single parameter variation in sensitivity assessments to assess two-way interactions and Monte Carlo simulations where all parameter values subject to variation are allowed to vary according to estimated or assumed probability distributions for the parameter values. The following is a list of variables where sensitivity analysis is likely to be particularly important.

Potential Parameters for Sensitivity Analysis

- Clinical phase costs
- Clinical phase success rates
- Clinical phase durations
- Peak-year net sales
- Annual net sales distribution characteristics (peak-year, rate of growth to the peak-year, effective patent life, erosion in sales after generic entry)
- Patient engagement distribution parameters for costs of implementation, reductions in out-of-pocket costs, and impacts on the development times and success rates

ADDITIONAL PATIENT ENGAGEMENT RESOURCES

- **CTTI Recommendations: Effective Engagement with Patient Groups Around Clinical Trials**
- **Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project**
- **Online Prioritization Tool**
- **Patient Group Engagement Across the Clinical Trial Continuum**
- **Patient Group Organizational Expertise and Assets Evaluation Tool**
- **Assessment of Patient Group Internal Aspect: Focus**
- **Assessment of Patient Group External Relationships: Other Patient Groups**

ABOUT THE CLINICAL TRIALS TRANSFORMATION INITIATIVE (CTTI)

The Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by Duke University and the U.S. Food and Drug Administration, seeks to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials. Bringing together organizations and individuals from across the enterprise—representing academia, clinical investigators, government and regulatory agencies, industry, institutional review boards, patient advocacy groups, and other groups—CTTI is transforming the clinical trials landscape by developing evidence-based solutions to clinical research challenges. Many regulatory agencies and organizations have applied CTTI's more than 20 existing recommendations, and associated resources, to make better clinical trials a reality. Learn more about CTTI projects, recommendations, and resources at **www.ctti-clinicaltrials.org**.

ABOUT TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

The Tufts Center for the Study of Drug Development (Tufts CSDD) is an independent, academic, non-profit research center at Tufts University School of Medicine in Boston, Massachusetts. Our mission is to provide data-driven analysis and strategic insight to help drug developers, regulators, and policy makers improve the quality, efficiency, and productivity of pharmaceutical R&D.

Established in 1976, Tufts CSDD conducts scholarly analyses addressing the economic, scientific, political, and legal factors that affect the development and regulation of human therapeutics. For over four decades, Tufts CSDD has been a prominent and influential voice in national and international debates on issues pertaining to biomedical innovation and the development of drugs and biologics. In addition, the Center hosts symposia, workshops, courses, and public forums on related topics, and publishes the *Tufts CSDD Impact Report*, a bimonthly newsletter providing analysis and insight to critical drug development issues.

ADDENDUM

FROM SECTION II
Primary Data Sources

- Clinical phase out-of-pocket costs by therapeutic class and molecule type (published literature and/or trial cost estimates built up from cost estimates of trial components such as trial sizes and per patient costs [e.g., data from Medidata Solutions, TrialTrove, R&D Statistical Sourcebook, clinicaltrials.gov])
- Development cycle times by therapeutic class and molecule type (pipeline databases; e.g., ADIS Insight, Clarivate Analytics, IQVIA New Product Intelligence, R&D Statistical Sourcebook, published literature)
  - Clinical trial performance and cost (**www.clinicaltrials.gov**; published literature)
  - Phase transition and clinical approval success rates by therapeutic class and molecule type (pipeline databases; e.g., ADIS Insight, Clarivate Analytics, IQVIA New Product Intelligence, R&D Statistical Sourcebook, published literature).
  - Peak-year and lifecycle sales by therapeutic class and molecule type (EvaluatePharma, ADIS Insight, Clarivate Analytics, published literature)
  - Effective tax rates (company financial statements and reports)
  - Cost of capital (published literature, new calculations from public data on industry stock market returns, debt-equity ratios, risk-free rate of return, corporate tax rate)
  - Effective patent life (published literature and calculations by therapeutic class)
  - New sales erosion rates after generic entry (published literature)

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