Significance

Despite allocating more than $11 billion each year to support clinical research, the system of federal funding for medical research lacks a coordinated approach for allocating resources based on the potential to close important knowledge gaps(1). Faced with limited budgets, organizations that support and fund clinical research must select and prioritize the most promising studies; however, the best methodological approaches to explicitly and systematically prioritize research in a real world setting are only beginning to be thoroughly explored.

Prioritization of federal funding is particularly critical in cancer research given its large human and economic burden. Cancer is the second leading cause of death in the United States with estimated annual economic costs exceeding $200 billion(2). Furthermore, government sponsorship of medical research is particularly prevalent in oncology, where the National Cancer Institute (NCI) funds approximately half of all cancer clinical trials, in large part through the National Clinical Trials Network (NCTN)(3). NCTN studies fill a critical gap in evidence generation left by industry and individual institutions by conducting head-to-head studies, evaluating combinations of treatments, studying rare cancers, and publishing negative research findings about therapies used in practice. Over the last 50 years, the NCTN has contributed to significant advances in the treatment and prevention efforts and has been instrumental in setting standards for clinical care.

Despite these considerable accomplishments, the NCTN faces a major challenge in the selection and prioritization of future clinical trials(4). Although the costs of conducting clinical trials and the number of individuals being diagnosed and dying from cancer have continued to rise(5); the NCTN faces a declining budget in real terms, which makes trial funding decisions increasingly difficult and strained. In a landmark report the Institute of Medicine (IOM) maintained that **"prioritization and selection of trial concepts is critical to ensure that limited public funds are used in ways that are likely to have the greatest impact on patient care**" and specifically recommended that trial proposals be rigorously and systematically evaluated and ranked against each other(6). Despite calling for such a considerable change – trial proposals currently undergo a primarily qualitative review process - the IOM report did not endorse or recommend any specific strategies for implementing a rigorous and systematic prioritization process.

Setting priorities for future research is a complex process that has received considerable recent interest(7-9). Portfolio management, a popular method in industry for managing and maximizing the value from a portfolio of investments, may help with selection and prioritization of cancer clinical trial investments. The key principles of portfolio management evolved from modern portfolio theory, a technique used to maximize a financial investment's expected return subject to a budget and overall risk constraint. Whereas modern portfolio theory derives estimates of risk and return from a stock's historical market performance, portfolio management expands the approach to fields outside of finance by redefining measures of risk and return appropriate for the specific setting.

Portfolio management is particularly well suited to managing and prioritizing publicly funded cancer clinical trial proposals because the approach can efficiently summarize both the expected risk and return of all potential investment decisions. Data from an entire portfolio can illuminate tradeoffs between risk and return that may be obscured when projects are reviewed independently, and can provide context to aid prospective decisions. The key challenge in using portfolio management techniques to evaluate NCTN proposals is in defining measures of risk and return that reflect the societal perspective appropriate for a government-sponsored funding agency and efficiently estimating these metrics across an entire portfolio of study proposals. **The overall goal of this proposal is to address this challenge by developing and evaluating methods to efficiently estimate critical measures of study performance, specifically risk (Aim 1) and return (Aim 2), and explore whether using these metrics within a 'portfolio management' framework to select trials could improve the efficiency of trial approval decisions (Aim 3).**

Aim 1. To predict the risk of a clinical trial failure.

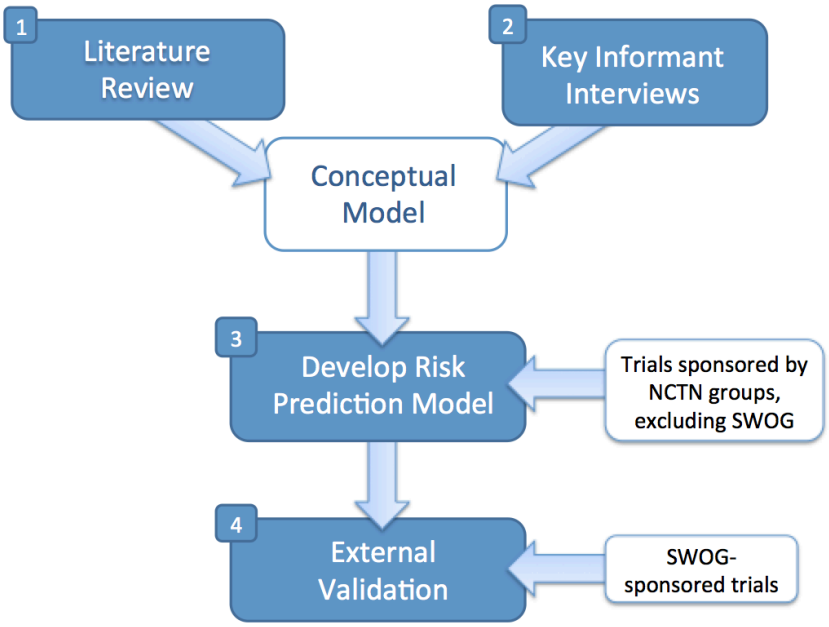
Rationale. A publicly funded clinical trial "fails" if it closes early and without sufficient accrual to address the primary endpoint as such trials are ultimately unable to inform clinical practice or benefit patients. The vast majority (nearly 90%) of early trial terminations are attributed to poor accrual(10), though factors such as drug shortages or external data that changes standard of care can also lead to an early trial termination. Assessing trial feasibility is of critical importance as nearly 1 in 3 NCTN-sponsored clinical trials close early

and are unable to address the primary endpoint, representing a tremendous waste of human and economic resources(10, 11).

A few studies have collectively investigated whether a limited set of trial characteristics are associated with the trial's ultimate success(12-14). The findings from these studies were both inconclusive, due in large part to small sample sizes in which these risk factors were evaluated, and importantly limited in scope with respect to the predictors studied. I propose to further previous work in this area by: (1) evaluating a more comprehensive list of trial characteristics, (2) testing whether these factors are associated with trial failure in a larger sample of clinical trials, and (3) combining these factors into a prediction model that can estimate a future trial's expected risk of failure using a single, objective, and quantitative measure as specifically recommended by the IOM report(6).

Approach. The overall approach of Aim 1 is summarized in Figure 1. I will develop a comprehensive conceptual model of clinical trial failure using a systematic literature review and key informant interviews, and then use this conceptual model to inform the development of a statistical model to predict the risk of a clinical trial failure. Lastly, I will evaluate the performance of this model in an single NCTN cooperative group, SWOG, that was not included in the initial model development.

Figure 1: Overview of approach for Aim 1



Step 1: Hypothesis generating literature review. A systematic literature review will be conducted to capitalize on the prior literature regarding clinical trial feasibility challenges. I will re-conceptualize general barriers to clinical trial participation [e.g. concerns about costs or adverse side effects (15-19)] as trial-specific factors, and formulate hypotheses about how important differences in these factors across trials may explain why certain trials fail and others do not. Data will be analyzed using an informal thematic synthesis(20), which is well suited to summarizing qualitative research for hypothesis generation.

Step 2: Key informant interviews. I will interview members of SWOG's Executive and disease committees to elucidate the perceptions and opinions of trial feasibility directly from those who conduct and participate in trial reviews. Interviews will follow a semi-structured guide that will include both 'open-ended' ended questions to elicit their experiences evaluating trial feasibility and probing questions to explore informants' perceptions and opinions regarding specific hypothesized factors identified from the literature review(21). The interviews will be transcribed and analyzed using an inductive coding approach(22, 23), a systematic method to analyze qualitative data where the analysis is guided by specific objectives. Specifically, after each interview I will generate a list of ideas and concepts related to trial feasibility and group these into preliminary descriptive themes; interviews will continue until no new themes emerge (i.e. data saturation).

Step 3: Development and evaluation of a statistical prediction model. Logistic regression analyses will be used to explore the association between clinical trial failure and candidate predictors identified from the final conceptual model. The primary data source for these analyses will be ClinicalTrials.gov, a comprehensive registry of publicly and privately funded trials that includes up-to-date accrual and reasons for early termination if applicable(24-27). The sample will include all Phase II-III clinical trials sponsored by the NCTN (excluding SWOG; see step 4) activated between 2002 and 2011 (n~500).

The primary outcome, a trial feasibility failure, will be defined separately for completed and active trials (currently active trials are included to avoid biasing the sample). For completed trials, trial success or failure is captured directly in the *clinicaltrials.gov* database. For trials that remain active at the time of

analysis, trial failure will be defined as trials with accrual status <50% of the target accrual (and alternative cut points will be explored in sensitivity analyses).

Candidate predictors will be formulated from the final conceptual model. Importantly, the clinicaltrials.gov database includes a broad and comprehensive collection of trial features about the majority of federally and privately funded late-phase cancer clinical trials conducted in the last decade, and thus will allow for novel exploration of predictors associated with the broader landscape of clinical trials (e.g. the number of concurrent trials available to a specific patient population). I also plan to link additional data sources to the clinicaltrials.gov database in order to explore a wide range of potential predictors. For example, linking the disease studied to the Surveillance and Epidemiology and End Results (SEER) database will enable calculation of the trial's sample size relative to the number of available cases in the US. Similarly, linking the intervention(s) studied to the FDA approval database would provide important information regarding the timing and type of FDA review.

The set of predictors to be included in the final model will be selected using data-dependent methods in which the final model is chosen by optimizing an information criterion derived from the log-likelihood. Bootstrap correction (whereby the entire model building exercise will be replicated within each bootstrap sample) will be used to internally validate the model and correct for potential overfitting(28).

Step 4: Externally validate risk prediction model. Trials conducted by a single cooperative group, SWOG (n~100), that were excluded from the initial model development (step 3) will be used as an external validation dataset to evaluate the predictive performance of the risk prediction model. Specifically, I will summarize the model's discrimination using the area under the receiver operating characteristic curve (AUC) and calibration by comparing visually the observed and predicted risks across deciles of predicted risk in a calibration plot and by calculating Hosmer-Lemeshow's X^2 statistic(29).

Innovation. The results from Aim 1 should improve our understanding of publicly-sponsored cancer clinical trial failures and could help researchers understand how trial design decisions influence completion rates. Aim 1 is innovative in its plan to leverage and link multiple independent data sources in order to evaluate a more comprehensive set of predictors. It is also innovative in the plan to develop a prediction model that, if successful, would provide single quantitative estimate of the overall feasibility risk for a clinical trial before it is launched. The findings from this analysis should therefore be generally useful to clinical trialists and funding agencies reviewing clinical trial proposals.

Aim 2: To determine the feasibility and acceptability of estimating the societal return of a clinical trial using minimal modeling VOI.

Rationale. Value of information (VOI) analysis is a quantitative approach to valuing research that has received increased attention, particularly within the context of comparative effectiveness research(30). This approach uses tools from economic theory and decision analysis to estimate the humanistic and economic value of performing additional research to better understand the safety, efficacy, and cost of technologies and medical interventions(31, 32).

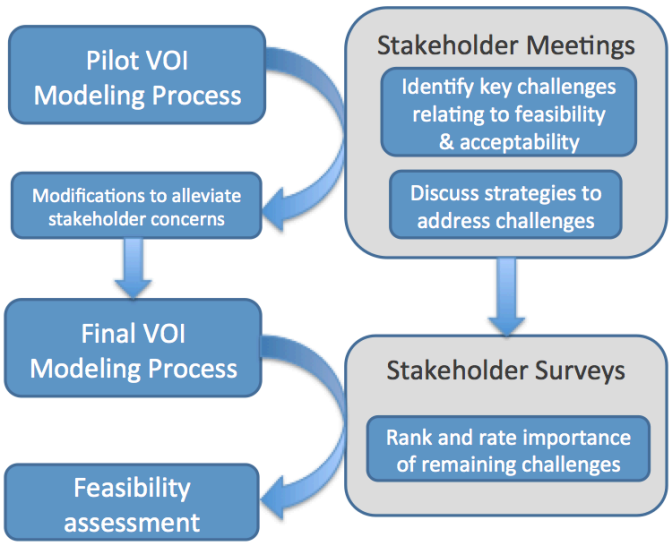
Unfortunately, traditional approaches to estimate VOI are time and resource intensive, severely limiting the real-world application of these methods. To date, there has been only one published example of implementation of VOI to inform research prioritization in the US, which was conducted by members of this dissertation's committee(33). Importantly, this implementation analysis also critically showed that providing VOI estimates to decision makers resulted in important changes in their priority rankings of research topics across a range of cancer genomic applications(33).

Minimal modeling VOI is a novel approach to estimate VOI with substantially less investment then traditional methods(34). Despite considerable interest from the Agency for Healthcare Research and Quality (AHRQ) and the Patient Centered Outcomes Research Institute (PCORI)(35, 36), the methods are only beginning to be used in an applied settings and the key challenges associated with such use fully explored. To address this knowledge gap, I therefore propose to develop an efficient and reproducible process for generating VOI estimates using minimal modeling across SWOG's portfolio of clinical trials, and assess the feasibility and acceptability of this process from the perspective of key stakeholders and decision makers.

Approach. I will follow an iterative mixed-methods approach for Aim 2 to engage stakeholders at various stages in the development and evaluation of the minimal modeling VOI processes (Figure 2).

Minimal modeling VOI can be defined as approaches that model VOI without constructing a decision model of the disease and treatment process to characterize the uncertainty in net benefit associated with an intervention(37). Minimal modeling is feasible when there is data on the net benefit for the interventions examined or sufficient data on health outcomes, costs, and their variances, such that full models are not needed. Cancer treatments are well-suited for minimal modeling techniques given the general availability of prior studies in cancer (e.g., Phase I, II, and III), economic information (example: SEER cancer registry linked to Medicare claims) and the detailed processes involved in gathering that data to generate a study proposal. Development of the minimal modeling approach will include ~10 case studies (i.e. trial proposals recently reviewed by SWOG). The approach will involve the following steps: 1) data collection; 2) generate VOI estimates; and 3) format results for presentation to the decision-makers and will be explored using a sample of.

Figure 2: Overview of approach for Aim 2



Step 1: Data collection. Data for each VOI topic will be collected from the prior studies, expert opinion, and/or generated using limited modeling. Table 3 identifies the data typically needed to inform the minimal modeling process.

Step 2: Generating VOI Estimates. The primary concept underlying VOI is that if decision makers had perfect information about the risks, benefits, and costs of a particular intervention, they would always be able to make correct choices regarding its use. The difference between the value of having perfect information and the value of current information (with attendant uncertainty) is known as the expected value of perfect information (EVPI). Whereas EVPI is an upper bound on the return from further research, the expected value of sample information (EVSI) represents the expected value of research from an actual study, e.g., of limited sample size. I will calculate EVPI and EVSI following the methodological approach described in detail in an AHRQ's Methods Future Research Needs Report(37).

Table 3: **Inputs Used for Minimal Modeling Approach for VOI Estimation (copied from PCORI grant proposal)**

1.	**Sample parameters**
a.	Proposed sample size of trial.
b.	Number of patients to be assigned to the new and comparator treatments.
c.	Demographic data, including age and gender.
2.	**Effectiveness parameters**
a.	Estimated probability of 'survival' (overall or event-free survival, stated as life years) for each treatment and comparator. Mean survival and standard error is based previous studies or elicited following methods described by Hiance et al 2009.(38)
b.	Optional: Estimated probability of 'survival with adverse events' over the time horizon of the model for each treatment and comparator.
3.	**Parameters related to the costs of the trial and medical treatment**
a.	Estimate of fixed trial costs based on the study proposal.
b.	Mean variable treatment-related costs per patient for each treatment and comparator. The standard error may be taken as 25% of the mean, if no data are available to inform this parameter.
4.	**Other parameters**
a.	Effective lifetime of use of the technology: Can be based on. the observed lifetime of similar technologies/treatments, or on expert opinion.
b.	The value of outcome (e.g., disease free survival, years of life, QALY) saved; for example see a survey of oncologists by Nadler et al.(39) Base value can be adjusted based on preferences of the funding agency.
c.	Population that could benefit from the trial results. Based on the initial prevalence of the disease, disease incidence over the effective lifetime of the technology, minus number of patients included in the proposed trial.
d.	Implementation (uptake) rate for the technology over time.(40-42)

Step 3: Format for Presenting the VOI Minimal Modeling Results: Lastly, a template for presenting the VOI to decision makers will be developed. The initial template will include the following elements: (1) Key input parameters from Table 3; (2) VOI calculations (EVPI and EVSI); and (3) brief reference descriptions (e.g., definition of EVPI in words).

Engaging stakeholders in the VOI development and assessment of feasibility. I will engage two stakeholder groups: SWOG Statisticians and Executive Committee members, as they represent two unique yet complimentary viewpoints in current trial proposal reviews. Specifically, I will conduct stakeholder meetings with each of these groups that will introduce VOI and minimal modeling methods generally, describe the provisional protocol for generating VOI estimates for SWOG trials, and present several applied examples (i.e. the case studies). During the meeting, I will clarify issues and explore stakeholders' concerns about the feasibility and acceptability of the proposed VOI methods and results. The meeting will be recorded and transcribed and a targeted qualitative thematic analysis(22) will be used to identify the major barriers and facilitators to using minimal modeling techniques in this setting, which will inform modifications to the modeling processes. Lastly, I will distribute a final report to stakeholders that includes a summary of the modifications and updated results and presentation of the case studies. I will then ask the stakeholders to complete a brief online survey. Using a 5-point Likert scale, stakeholders will be asked to rate the importance of the various barriers and concerns initially identified at the meetings, their perceptions of the modifications employed to alleviate these concerns, and their confidence in minimal modeling methods overall, as well in each of the case studies.

Innovation. Aim 2 proposes to explore an innovative new approach to estimating VOI, and in so doing, will enhance our understanding of minimal modeling. If the applicability of minimal modeling is found to be limited, the findings from Aim 2 will provide a comprehensive assessment as to the chief reasons why, which could help target future methodological work in this area. If minimal modeling approaches are found to be broadly feasible and acceptable, then these approaches could be used prospectively in this setting, and potentially others, to improve research prioritization efforts.

Aim 3. To explore whether using a portfolio management framework to select trials could improve the efficiency of trial funding decisions.

Rationale for Aim 3. While ranking across either expected risk or return is relatively straightforward, it is often difficult for decision makers to prioritize potential investments across multiple metrics without additional quantitative tools. Portfolio management brings together measures of risk and return into one combined model and, in so doing, allows decisions makers to evaluate their decisions on both metrics across all trial proposals in the portfolio simultaneously.

I propose to compare SWOG's current portfolio performance to the hypothetical performance of alternative portfolios that could have been realized had different trials been selected for funding. In other words, I will seek to answer the question: had decision makers at SWOG chosen to fund a different set of trials, could they have improved the efficiency of their portfolio?

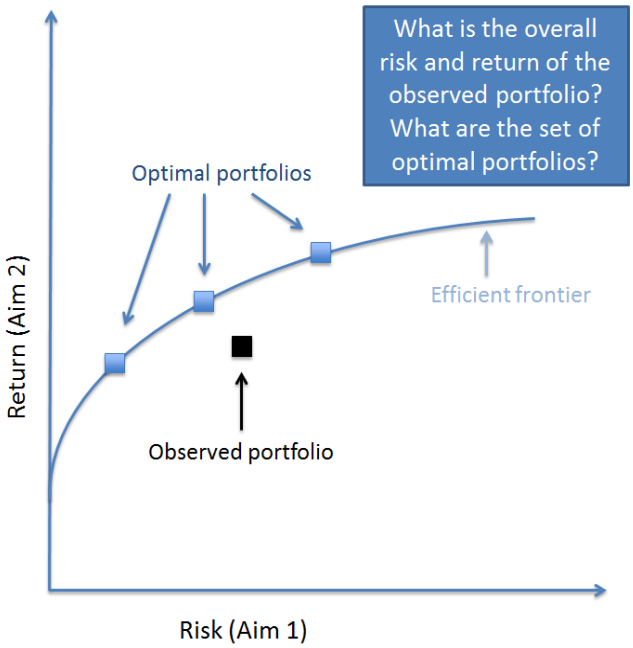
An efficient portfolio is defined as an allocation of investments that yields the highest expected return for a given level of risk. The set of all efficient or optimal portfolios are those represented along an efficient frontier. An efficient fronteir represents the upper edge of a region represented by plotting every possible combination of investments according to their overall expected risk and return (see Figure 3). Portfolios along the efficient frontier each represent different investment preferences (e.g. risk averse or high risk); each is 'optimal' in the sense that there is no ability to improve returns without increasing risk (or conversely decrease risk without also decreasing returns).

Approach. To represent alternative portfolios of clinical trials, these analyses will include a sample of phase III interventional trial proposals reviewed by SWOG in 2013 (n~25), including those that were approved and those that were not. Predicted risk and return (i.e. EVSI) will be obtained from the models developed in Aims 1 and 2. If I am unable to predict the risk, options such as multiple imputation techniques or modifying the prediction model to omit certain variables will be explored. If I am unable to generate EVSI estimates using minimal modeling, a full decision modeling approach will be used. In the unlikely event that more than five full decision models would be required across the initial sample, I will restrict the analyses to a sample of proposals from a single disease site (e.g. breast or gastrointestinal) to increase efficiency in generating VOI estimates using full decision models. The set of optimal portfolios will be identified using an an integer programming optimziation model(43), presented below:

Maximize Expected Return of Portfolio: $\sum_{i=1}^{N} x_i * v_i$
Subject to the following constraints:
$\sum_{i=1}^{N} x_i \leq$ budget constraint
$(\sum_{i=1}^{N} x_i * r_i) / \sum_{i=1}^{N} x_i \leq$ risk threshold (varies)

Where:
$x_i = \begin{cases} 1 \text{ if trial } i \text{ is selected for funding} \\ 0 \text{ otherwise} \end{cases}$
v_i = expected return (ENBS) of trial proposal *i*
r_i = predicted risk of trial proposal *i*

Figure 3: Hypothetical results from a portfolio evaluation



The overall risk and return of the observed portfolio (i.e. the set of trials that were approved by SWOG) will be compared to the set of optimal portfolios in a risk-return plot (see Figure 3 for an example). ***I hypothesize that the observed portfolio will be suboptimal; all else being equal, funding a different set of trial proposals would have yielded a higher expected return, lower risk, or both.*** A secondary objective of these analyses will be to explore how the rankings of trial proposals change when ranked according to (i) expected return (EVSI), (ii) predicted risk, and (iii) risk-adjusted return. The goal is to explore whether jointly accounting for value and risk leads to importantly different rankings than consideration of either metric alone and to determine how well these rankings align with SWOG's initial review process.

Innovation. The results from Aim 3 will explore the potential improvements in efficiency attained with portfolio management techniques. If found to be useful, the scope of these analyses could be extended, by evaluating a more complete sample of the research portfolio and/or incorporating more realistic constraints. Lastly, if successful, similar portfolio management approaches could be extended to settings both within and beyond cancer to improve the efficiency of funding decisions in other healthcare research organizations.

Dissemination Strategy

An essential aspect of this dissertation proposal is to work collaboratively with stakeholders throughout the process, which should ensure that the results from these analyses are meaningful and ultimately adoptable by the relevant decision makers. In addition, I have been invited to present the interim and final results to SWOG members at their twice-yearly group meetings. Lastly, I will make publicly available all of the models and tools developed as part of this dissertation, and will publish the results of these analyses in traditional academic journals to disseminate the results to a wider audience of potential decision makers.

Timeline

	2014			2015		
	Spring	Summer	Fall	Winter	Spring	Summer
Aim 1 Activities						
Conduct Systematic Literature Review	■	■				
Conduct Key Informant Interviews			■			
Build and Evaluate Prediction Model				■		
Aim 2 Activities						
Develop Process of Minimal Modeling VOI		■	■	■		
Evaluate Feasibility of Minimal Modeling VOI			■	■	■	
Aim 3 Activities						
Evaluate Observed vs Optimal Portfolios						■