Prioritizing research: the use of risk prediction, value of information analyses, and portfolio evaluation to improve public investments in cancer clinical trials

Caroline Savage Bennette

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Reading Committee:
David L. Veenstra
Scott D. Ramsey
Anirban Basu
Josh C. Carlson

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Abstract

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Chair of the Supervisory Committee:
Professor David L. Veenstra, PharmD, PhD
Professor of Pharmacy
Department of Pharmacy

Background: Fewer than half of all medical interventions in use today are supported by clinical evidence. Despite allocating more than $11 billion each year to support clinical research, federal funding for medical research lacks a coordinated system for prioritizing and allocating resources to efficiently address these important knowledge gaps. The Institute of Medicine recently stressed that rigorous prioritization of trial concepts for large cancer clinical trials cooperative groups was critical to ensure that limited public funds are used effectively and efficiently. Yet despite this ardent call to improve the means of prioritizing and selecting cancer clinical trials, many questions remain about how to achieve these

goals. Portfolio management is a systematic approach to decision-making that is widely used in the private sector to inform and manage research investments. Yet despite it's conceptual simplicity, this approach has not been used to inform publicly funded cancer clinical trial investments because of the difficulty in defining and measuring risk and return in this setting. In this dissertation, I therefore developed and evaluated quantitative measures of risk and return that were appropriate for National Clinical Trials Network-sponsored trials and applied a proof of concept portfolio evaluation approach to a sample of clinical trial proposals recently reviewed by a large cancer clinical trials cooperative group, SWOG.

Methods: In Chapter I, I developed a statistical model to predict the risk of an accrual feasibility failure, defined as a trial that does not enroll a sufficient number of patients and consequently is unable to inform clinical practice patterns, based on trial-level variables available before the trial is launched, and evaluated its internal validity. In Chapter II, in collaboration with key stakeholders I developed a process to efficiently quantify the societal return of the proposed studies using Value of Information (VOI) methods and evaluated its feasibility and acceptability. Lastly, in Chapter III, I estimated the predicted risk and expected return for a sample of recently reviewed clinical trial proposals to illustrate how a portfolio management framework could inform funding decisions within a cancer clinical trials cooperative group setting.

Results: In Chapter I, I provide a comprehensive and empirical assessment of risk factors that are associated with and predictive of a clinical trial that does not meet

50% of its target accrual. I identified several novel predictors, and showed that these predictors in combination with several established risk factors could predict which NCTN-sponsored clinical trials were at highest risk of poor accrual. In Chapter II, I describe several key changes that I made to the traditional Value of Information analysis framework to accommodate SWOG stakeholders preferences and facilitate timely calculation. The efficient and pragmatic process that I developed leveraged information included in each trial proposal and reported the expected health benefits and incremental healthcare costs associated with acquiring additional information separately. In Chapter III, I illustrate how a portfolio management approach provides a means of efficiently summarizing both the expected accrual feasibility and societal return – two critical criteria - for a large sample of trial proposals simultaneously and therefore provides a framework for evaluating trial concepts against one another.

Conclusions: I found that a portfolio evaluation is a feasible and potentially useful response to the IOM's call for more systematic approaches to select and prioritize trial concepts against one another. The approach can facilitate the ranking of a large number of trial concepts simultaneously using two key criteria for which I developed novel methods to estimate, and also inform longer-term strategic decision-making. A portfolio evaluation approach could therefore help decision makers select and prioritize cancer clinical trial concepts that have the greatest potential to improve population health and thereby optimize the return on limited research funds.

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Chapter I

Predicting poor accrual in oncology trials: an empirical evaluation in the National Clinical Trials Network (NCTN) portfolio

Caroline S Bennette, Scott D Ramsey, Cara McDermott, Josh J Carlson, Anirban Basu, David L Veenstra

Abstract

Introduction: A recent Institute of Medicine report stated that improving the prioritization and completion rates of trials within the largest network of clinical trials in cancer, the National Clinical Trials Network (NCTN), is critical to ensure that scientific advances are translated into clinical benefits for patients. Although many studies have investigated the perceived barriers to accrual from the patient or provider perspective, the extent to which differences in trial-level factors could predict poor accrual has not been comprehensively evaluated. The purpose of this study was to investigate the empirical relationship and predictive properties of a broad set of putative risk factors of poor accrual among NCTN-sponsored trials.

Methods: The study sample included 787 phase II and III adult NCTN-sponsored trials that opened between 2000 and 2011. Poor accrual was defined as trials that closed with only or were currently accruing at <50% of target. Candidate risk factors were identified from a literature review and interviews with clinical trials experts. A multivariate logistic regression model was developed to predict poor accrual. The model's performance was evaluated by assessing calibration and discrimination via the area under the curve (AUC) and corrected for statistical optimism using bootstrap resampling methods.

Results: 145 (18%) NCTN-sponsored trials closed due to poor accrual or were accruing at <50% of target 3 years or more after initiation. Factors that predicted poor accrual included: the number of competing trials, proportion of the eligible patient population planned for trial enrollment, the annual incidence of the patient population, trial phase, sample size, evaluation of multiple clinical conditions, a common solid tumor, and whether the trial evaluated a new investigation agent, targeted therapy, radiation therapy, or required a biopsy or tissue sample to assess eligibility. Collectively these factors showed good calibration and discrimination (bootstrap corrected AUC: 0.734; 95% CI: 0.689, 0.780) for predicting trials that would experience poor accrual. Results were robust to different definitions of accrual success and model selection strategies.

Conclusions: This study is the first to characterize the empirical relationship between a comprehensive set of putative trial-level risk factors and poor accrual within the NCTN portfolio. We identified several important predictors that may independently provide decision makers with useful information when reviewing trial accrual feasibility. Furthermore, a simple risk prediction tool based on 11 risk factors could be useful in quantifying the likelihood of poor accrual for

prospective trials, if validated prospectively. Such a tool could inform trial design, aid prioritization decisions, and help target limited resources to support accrual where most needed.

Introduction

A 2010 report by the Institute of Medicine (IOM) stressed the need for a more systematic approach to prioritize the selection of cooperative group-sponsored clinical trials and improve recruitment and trial completion rates(1). The report prompted the transformation of the Cooperative Group program into the National Clinical Trials Network (NCTN) in March 2014 in an effort to create a more streamlined and efficient system for developing and managing cancer clinical trials(1, 2). Although the consolidation and centralization of the group's activities will likely improve efficiency, many questions still remain about how to prioritize trials and improve recruitment rates.

Low accrual to adult oncology clinical trials is a major barrier to progress in cancer therapy. Clinical trials that do not achieve sufficient accrual are frequently unable to inform clinical practice or benefit patients(3-5). Moreover, low accruing clinical trials often represent a waste of scarce human and economic resources(6).

Identifying factors that predict poor accrual in trials before they are launched could inform prioritization efforts and help target limited resources to support accrual where it is most needed. Although many studies have investigated the perceived barriers to accrual from the patient or provider perspective(7, 8), the extent to which differences in trial-level factors could predict poor accrual has not been comprehensively evaluated. The few prior studies that have explored trial characteristics associated with accrual were importantly limited in the breadth of candidate predictors and number of trials included in the sample(5, 9). The purpose of this study was therefore to empirically evaluate the association and predictive properties of a broad set of putative trial-level factors and poor accrual within the portfolio of late-phase NCTN-sponsored clinical trials.

Methods

Data Sources and Study Population

The primary data source for these analyses was the recently created AACT (Aggregate Analysis of ClinicalTrials.gov) database, a reformatted database of clinical trials registered in ClinicalTrials.gov. Details on the construction of the AACT have been reported previously(10). We downloaded the 2013 AACT database and abstracted all interventional, late-phase (II or III) adult oncology trials started between 2000 and 2011 with at least one member of the NCTN listed as a sponsor or collaborator (n=810). The AACT database includes enrollment data for most completed studies. We obtained accrual data for ongoing trials directly from individual cooperative groups and the Clinical Trials Support Unit (CTSU), a system that manages the enrollment process and patient entry onto NCI-sponsored cancer clinical trials on May 15, 2014.

We combined the AACT database with several additional data sources to be able to explore a broader set of potential risk factors associated with poor accrual. First, we obtained dates of initial marketing approval and the type of initial FDA review (standard or priority) for all drugs and biologicals evaluated in each trial from the FDA database of approved drugs, Drugs@FDA {www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm}. Second, we obtained annual US incidence of each cancer condition studied in an NCTN-sponsored clinical trial from the Surveillance, Epidemiology, and End Results (SEER) database(11).

Outcome: Poor Trial Accrual

We defined the outcome of our analyses, poor trial accrual, as a trial that terminated or closed with substantially lower than planned accrual and was therefore unlikely to address the primary endpoint. For our primary analyses we classified trials as having poor accrual if their actual accrual was <50% planned enrollment given prior evidence that very few trials with <50% at one year post activation ultimately attain sufficient accrual. Additionally, accrual <50% beyond the first year currently triggers a formal review and possible early termination by CTEP(12, 13). We also considered alternative thresholds (25% and 75%) in sensitivity analyses. For trials that remained open and recruiting at the time of analysis, we classified trials by their accrual rate to date. Lastly, we reviewed the reasons for early termination and excluded trials that closed early due to interim results or toxicity issues (n=23). Table 1 summarizes the outcome of all trials in our study, separately for studies that were completed or ongoing at the time of these analyses.

Developing a Conceptual Model of Poor Trial Accrual

We used a thematic synthesis approach to identify and synthesize evidence regarding trial-level risk factors for poor accrual barriers from a literature review and key informant interviews with clinical trial investigators(14). We used a purposeful rather than exhaustive sampling strategy on the basis that the results of a conceptual synthesis will not change based on the number of studies that contain the same concept, but will depend on the range of concepts found(14).

We focused our literature search on either (a) previously published reviews regarding barriers to accrual in cancer clinical trials, or (b) studies on accrual challenges specifically within a cooperative group or network setting. Full details of our search strategy and the key findings from each study are included in the Appendix. We identified 38 studies that met our inclusion criteria of which 15 were included in our final analysis and review. We conducted key informant interviews (n=3) with experts involved in trial design, management, and recruitment, including

nationally recognized experts who each had several decades of experience leading trials and investigators who had experience enrolling patients onto a diverse portfolio of clinical trials. Each interview used a semi-structured interview guide [see Appendix] and began with a brief introduction to our study objectives, followed by a period of open-ended and probing questions regarding their experiences with accrual challenges and the key factors they felt were responsible, and concluded by asking for their comments and feedback on the initial conceptual model of factors associated with inadequate accrual that was developed from the literature review.

The thematic synthesis consisted of three iterative and overlapping stages of analysis. First, we abstracted the key findings from each study in our literature review and key informant interviews that related to factors that could potentially differ between trials and therefore act as trial-level risk factors. Second, we organized these findings into related areas to create descriptive constructs. Lastly, we organized these constructs by overarching themes related to: (a) the broader landscape in which the trial would be launched, (b) the disease(s) and treatment(s) being evaluated, and (c) the trial's design. The final conceptual model is shown in Figure 1.

Selecting & Measuring Predictors of Successful Trial Accrual

We attempted to identify or derive measureable candidate predictors to represent all putative factors of accrual success included in our conceptual model. Some predictors (e.g. whether the trial was conducted in a metastatic or adjuvant setting) were straightforward to measure whereas others (e.g. complexity of eligibility criteria or less compelling scientific rationale) were more difficult or not feasible to quantify with currently available data. The final set of candidate predictors was therefore limited primarily by the availability of systematically recorded data and included the factors listed in Table 2.

We classified interventions for each trial as FDA approved if the first approval date for the relevant drug or biological preceded the start date of the trial; surgical or radiotherapy interventions were considered FDA approved for the purposes of these analyses. Following the initial match between Drugs@FDA and the clinicatrials.gov database, we reviewed matches for quality assurance and manually updated several interventions that did not initially match due to misspellings or alternative names (e.g. company code names). We also verified that all interventions that did not match with the Drugs@FDA database were not yet approved by manually searching for each of the drug names or investigational numbers in PubMed and online.

To estimate the level of competition for patients we first manually classified the clinical condition(s) studied by each NCTN-sponsored trial and then identified all trials registered on ClinicalTrials.gov that studied the same clinical condition(s) using a text search algorithm. A full description of the algorithm and the results of the classification are included in the Appendix. Next, within each clinical condition we counted the total number of trials that opened in the year preceding the start date of the index NCTN trial (these were considered "competing" trials) and divided by the total annual incidence of the relevant patient population. If an NCTN trial evaluated more than one clinical condition we classified all trials with any overlapping conditions as competing trials, but also divided by the total incidence of all conditions.

Lastly, section 801 of the Food and Drug Administration Act of 2007 that required registration of trials initiated after September 27, 2007 or initiated before that date and still ongoing as of December 26, 2007 on ClinicalTrials.gov. Though there were many incentives to register trial before 2007, there was not a legal requirement and the portfolio of trials on ClinicalTrials.gov before 2007 may be incomplete. We therefore used bootstrapping and multiple imputation techniques to recalibrate the total number of competing trials that were launched prior to 2007. Full details of this approach as well as related sensitivity analyses are included in the Appendix.

Enrollment fraction was defined as the percentage of all eligible patients who would be enrolled in the trial each year if the trial accrued as expected. We calculated planned accrual as the total planned accrual divided by the planned duration of the trial and then divided by the annual incidence of the relevant patient population. Additional details regarding the measurement of all putative risk factors included in the model and the specific construct(s) from the conceptual model that each is intended to capture are included in the Appendix. To minimize overfitting of models, no exploratory search beyond the *a priori* predictors derived from the conceptual model was performed.

Statistical Analyses

We used univariate and multivariable logistic regression models to explore the association between trial accrual success and each risk factor identified from the conceptual model. We developed a prediction model by selecting from among all candidate predictors a parsimonious set by optimizing the Aikaike Information Criterion (AIC). We also explored how different selection criteria would impact the final model. We evaluated the discrimination of the predictive model by calculating the area under the receiver operating characteristic curve (AUC) and the calibration by comparing visually the observed and predicted risks across deciles of predicted risk in a calibration plot. Predictive accuracy was corrected for overfit ("optimism") by

bootstrap resampling with 200 replications wherein the predictors were chosen by optimizing the AIC in each replication. All statistical analyses were conducted using Stata 13.0 SE (StataCorp LP, College Station, Texas).

Results

Overall, 145 (18%) NCTN-sponsored trials closed with poor accrual or were accruing at <50% of targeted accrual at the time of these analyses. Table 2 summarizes the characteristics of trials with successful and poor accrual. Trials with poor accrual tended to be launched amidst a higher number of competing trials (4.0 vs 2.8 per 10,000 eligible patients) and have a higher enrollment fraction (planning to enroll 0.068% versus 0.031% of the eligible patient population each year) than those with successful accrual. Trials with poor accrual were also less likely to study a new investigational drug (17% versus 31%), a targeted therapy (25% vs 36%), use non-randomized designs (46% versus 59%), be earlier phase (58% vs 72% were phase II), or evaluate a greater number of clinical conditions or interventions, but were more likely to evaluate radiation therapy (32% vs 20%).

The multivariable model to predict poor accrual included the factors shown in Table 3. The discriminatory performance of the multivariate model was good (bootstrap corrected AUC: 0.734; 95% CI: 0.689, 0.780). Predicted risks of poor accrual were in good agreement with observed risks across the range of predicted risks, indicating good calibration (Figure 2). Trials in the top 10% of predicted risk had an average 50% predicted (47% actual) risk of poor accrual compared to a mean of 14% predicted (15% actual) among the remaining 90%.

Sensitivity Analyses

Our results were robust to different definitions of poor accrual. A total of 104 (13%) or 183 (23%) trials experienced poor accrual when classified as <25% or <75% target of planned enrollment, respectively. The changes in the multivariable models were omitting common cancers and annual incidence (<25% definition) or including a term for surgical or procedural intervention (<75% definition). The discriminatory ability was slightly improved with the stricter definition of poor accrual (bootstrap corrected AUC: 0.752) and slightly reduced with the less strict definition (bootstrap corrected AUC: 0.685). Our model was also robust to different criteria used to select the final predictors. When we selected predictors by their marginal contribution to the AUC, including all those with at least a 0.001 improvement, the final model was the same with the exception of omitting common cancers and annual incidence.

Discussion

Summary

We conducted a retrospective analysis of trial-level risk factors associated with poor accrual across the entire NCTN portfolio of phase II and III clinical trials launched in the last decade. We identified several important factors were importantly associated with poor accrual. Of note, this is the first study to our knowledge that has characterized the empirical relationship between the level of competition for patients and risk of poor accrual in cancer clinical trials. Taken collectively these trial-level risk factors were important predictors of a late phase clinical trial failing to achieve more than 50% of its targeted accrual.

Implications

A prediction tool for risk of poor accrual could inform trial design, aid in the selection and prioritization of clinical trials, and help target limited resources to support accrual where it is most needed. First, a quantitative measure of a trial's risk of poor accrual could be useful during the planning phase for accrual predictions. When available, accrual predictions are based on cooperative group experience in a particular setting; however, we identified several trial level factors that could importantly alter projections based on past experience. For example, trials that are launched in environments that are more competitive than the reference case may experience much higher rates of poor accrual than anticipated. Moreover, when previous accrual experience is not available, this prediction tool could help inform educated judgments regarding the likelihood of achieving certain accrual targets.

Second, the prediction tool provides an objective and quantitative summary measure of feasibility that can aid in the selection and prioritization of prospective trial proposals. Importantly, we identified a small subset of trials at very high risk of poor accrual: those in the top 10% of predicted risk (n=75) failed almost half the time and those in the top 5% (n=37) failed nearly 70% of the time. The extent to which such high risk trials should be pursued is a complex question that involves consideration of several criteria beyond feasibility; however, providing decision makers with an explicit measure of feasibility should help inform the sometimes necessary tradeoffs between these criteria.

Lastly, the prediction tool could help identify trials that have an increased risk of poor accrual so that limited funds and other resources could be targeted appropriately. The NCI currently reimburses providers for patients enrolled on clinical trials with a fixed capitation rate. Studies that are deemed complex according to several criteria, including feasibility, can receive additional funds that incentivize participation in these trials. The prediction tool for poor accrual could therefore serve as an adjunct to this process.

Comparison with other studies

Although numerous studies have investigated reasons for poor accrual to clinical trials, only a few have empirically evaluated predictors of accrual success. Schroen *et al.* evaluated several potential predictors of accrual feasibility using a convenience sample cooperative group trials launched between 1991 and 2004. Although they evaluated several of the same predictors as in the current analysis, they did not identify any factors conclusively associated with achieving sufficient accrual(12). Their inconclusive findings were likely due to a very small sample size – only 82 trials – compared to our sample of nearly 800 trials.

Cheng et al. identified several metrics associated with early accrual outcomes that were predictors of long-term accrual success(3). Such early warning signals may be useful for trial re-designs or decisions to terminate a trial that has already launched; however they are not useful in the prioritization or planning of trial concepts as such data are not available until after a trial has started. In contrast, we evaluated trial characteristics that were known or could be known at the time the trial was launched and could therefore be used in both the planning and prioritization and selection of trial proposals.

Korn et al. also found a lower rate of poor accrual among NCTN trials that evaluated an investigational new agent compared to those that did not(5). Among phase III trials activated between 2000 and 2007, they found that 18.5% with an investigational new agent and 26.7% without failed to achieve sufficient accrual. Surprisingly, the authors concluded that there was no substantial difference in the proportion of poorly accruing trials according to whether or not the trial involved an investigational new agent, despite a seemingly large and likely statistically significant difference. Our findings regarding the impact of studying an investigational new agent on accrual were similar, but our conclusions differ: we contend that they are important because accrual predictions based on trials of new investigational agents may not provide the best available prediction of accrual for trials of FDA-approved interventions and vice versa.

Limitations

This study has several important limitations that warrant discussion. First, we have not yet externally validated the model to predict poor accrual. Although we developed the model using several *a priori* candidate predictors and adjusted for statistical overfit with bootstrap correction, the model's primary benefit would be in predicting accrual risk for future trials. Thus an external validation of the model's performance in trials started after 2011 will be an important next step to confirm these results. It is also plausible that the prediction model could provide less accurate estimates than those that can be obtained already from clinical trialists and other stakeholders. It will therefore also be important to evaluate whether current assessments of trial

accrual feasibility align with the predicted risk of poor accrual and to the extent the tool might improve trial accrual predictions over the current proposal evaluation process.

Second, the majority of risk factors included in the prediction model are not modifiable and changes to those that are (e.g. sample size or whether the trial was randomized) will tend to affect more than just accrual. We did explore a broad range of putative modifiable risk factors; the finding that few of these were predictive of poor accrual suggests that their potential impact on accrual is context specific and therefore better addressed on a case-by-case basis. Thus the tool is likely limited in its ability to inform individual trial design choices; however, it can be used to estimate an individual trial's overall risk of poor accrual, which may inform more detailed and specific protocol-related design decisions.

Third, we classified trials as having poor accrual using a threshold of <50% planned or target accrual. This definition was informed by prior studies and current clinical trial stopping rules. We explored the robustness of this definition through several sensitivity analyses and found that a more or less strict definition of poor accrual would not importantly change the predictors included in our multivariable model, and would result in slightly improved or reduced discriminatory abilities, respectively.

We also found that there was a higher rate of poor accrual among completed trials than ongoing studies. It is therefore possible that our definition of poor accrual for ongoing trials may not capture the complete set of trials that will eventually terminate with <50% of targeted accrual; however, we felt that this was the most robust and least biased approach to classify trials with poor accrual. Prior studies have avoided this challenge by restricting the analyses to completed trials (3); however, this approach is subject to sampling biased because trials that terminate early due to poor accrual are more likely to be included in the analyses. Another recent study used time-to-event analyses to study the cumulative incidence of failing to complete(15); however, such an approach is not appropriate for identifying risk factors associated with accrual outcomes of different trials that operate on very different time scales. In other words, some trials plan to complete enrollment within a year, while others may take a decade or longer; an outcome of poor accrual identified earlier in shorter trials should not in itself be indicative of higher risk, but would within a time-to-event analysis.

Fourth, our conclusions are limited to late phase clinical trials supported by the NCTN. A more complete evaluation of accrual in a broader portfolio of cancer clinical trials is clearly warranted given what others have called an 'epidemic' of cancer clinical trials that fail to complete(15). Unfortunately, up to date accrual information is not currently well captured in the ClinicalTrials.gov database(16). We echo the call from Mitchell *et al.* for more detailed and timely information regarding accrual to be captured in ClinicalTrials.gov as a necessary first step

towards better understanding challenges and drivers of accrual across the entire portfolio of cancer trials(16).

Fifth, it is important to emphasize that the prediction model we developed should not be viewed as replacing decision makers' judgment when it comes to feasibility or trial prioritization for several reasons. Some key factors, such as the scientific rationale of the trial or relevance to clinical practice, are likely critical to accrual success, but are not currently measured in a systematic or standardized way and were therefore not included in our prediction model. Other factors, such as a trial's complexity or patient burden, are only captured imperfectly from available data. That said, our model integrates and consolidates key measurable factors that are associated with poor accrual into a single, objective metric and provides a framework and rationale for more research on the measurement and evaluation of additional trial-level risk factors associated with poor accrual.

Lastly, a trial's risk of poor accrual is only one of several criteria that are important to decision makers when reviewing and prioritizing clinical trial proposals. It will be interesting and important to consider how the predicted risk of poor accrual interacts with other quantifiable criteria, such as Value of Information (VOI) estimates, within a portfolio evaluation(17). This will be addressed more fully in Chapters 2 and 3.

Conclusions

We identified important and significant associations between several trial characteristics and poor accrual among NCTN-sponsored clinical trials, in particular the level of competition for patients, the enrollment fraction, whether the trial studied a new investigation drug, and the phase of the trial. We developed a prediction model that, if validated prospectively, could provide a rigorous and transparent measure to calculate the risk of poor accrual based on measurable quantities. Systematically considering the overall influence of these multiple factors could aid in the design and prioritization of future clinical trials and therefore provides a direct response to the IOM's call for efforts to improve the selection, support, and completion of publicly funded cancer clinical trials.

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Table 1: Summary of outcome classification, stratified by trial completion status.

	Trials with successful accrual (>50% of target) N=642	**Trials with poor accrual (<50% of target) N=145**
Trial enrollment ongoing	242 (38%)	36 (25%)
Enrollment completed	400 (62%)	109 (75%)

Table 2: Summary of trial characteristics for all NCTN-sponsored phase II or III oncology trials registered in ClinicalTrials.gov and started between 2000 and 2011. All values are median (IQR) or number (%). Factors included in the multivariate model are bolded.

	Trials with successful accrual (N=642)	**Trials with poor accrual** (N=145)
Number of competing trials (those that opened within a year of index NCTN in the same patient population, per 10,000 eligible patients)	**2.8 (1.0, 5.6)**	**4.0 (1.7, 9.4)**
Intervention modality*		
Drug or biological	590 (92%)	131 (90%)
Surgery or procedure	105 (16%)	27 (19%)
Radiotherapy	**129 (20%)**	**46 (32%)**
Multimodality	264 (41%)	70 (48%)
Intervention type		
Therapeutic	568 (88%)	127 (88%)
Non-therapeutic	74 (12%)	18 (12%)
Targeted therapy	**232 (36%)**	**36 (25%)**
New investigational agent	**199 (31%)**	**25 (17%)**
Intervention granted priority or fast track review by FDA**	363 (57%)	80 (55%)
Metastatic setting	131 (20%)	25 (17%)
Clinical Setting*		
Blood cancers (leukemia, lymphoma or myeloma)	107 (17%)	26 (18%)
Prostate, colon, lung, or breast tumors	250 (39%)	50 (34%)
All other solid tumors (not prostate, colon, lung or breast)	**287 (45%)**	**69 (48%)**
Annual incidence of eligible patient population	**76,100 (52,000 - 232,700)**	**64,990 (24,100 - 170,000)**
Enrollment fraction (%)	**0.031 (0.013, 0.090)**	**0.068 (0.022, 0.191)**
Sample size	**82 (51, 242)**	**110 (60, 468)**
Randomized design	264 (41%)	78 (54%)
Phase III	**179 (28%)**	**61 (42%)**
Placebo control	62 (10%)	10 (6.9%)
Trial Complexity & Patient Burden		
Number of interventions studied	2 (1, 4)	3 (2, 5)
More than one condition evaluated	**173 (27%)**	**54 (37%)**
Intervention assignment blinded	86 (13%)	18 (12%)
Number of sites enrolling patients	33 (7, 80)	48 (22, 100)
Eligibility limited by performance status	562 (88%)	126 (87%)
Eligibility limited by age	27 (4.2%)	4 (2.8%)
Tissue sample or biopsy required to assess eligibility	**267 (42%)**	**68 (47%)**
Total number of eligibility criteria	51 (39, 64)	49 (40, 61)
Length of follow up for primary endpoint (in years)	4.1 (2.1, 6.0)	3.4 (2.2, 5.2)
Any endpoint a toxicity or safety issue	244 (38%)	48 (33%)

*not mutually exclusive categories

**for any indication

Table 3. Multivariable Logistic Regression Model: Risk Factors for Poor Accrual to NCTN-Sponsored Phase II and III Trials Registered in ClinicalTrials.gov and Started Between 2000 and 2011.

Risk Factor	**Odds Ratio**	**95% CI**	**P value**
Number of competing trials per 10,000 eligible patients	1.74	1.26, 2.41	0.001
Radiation therapy	1.73	1.10, 2.72	0.018
More than one condition evaluated	1.93	1.20, 3.10	0.006
New investigational agent	0.38	0.21, 0.68	0.001
Targeted therapy	0.54	0.34, 0.87	0.012
Enrollment fraction [per 1%]	2.82	1.37, 5.80	0.005
Sample size [per 100 patients]	0.96	0.92, 1.00	0.040
Phase III (versus Phase II)	2.82	1.66, 4.80	0.0001
Biopsy or tissue sample required to assess eligibility	1.60	1.06, 2.43	0.025
Common solid tumor setting (prostate, breast, lung, colon)	2.11	1.14, 3.88	0.017
Annual Incidence of clinical condition(s) [per 10,000 patients]	0.97	0.95, 1.00	0.037

Figure 1. Conceptual model of factors associated with poor trial accrual.

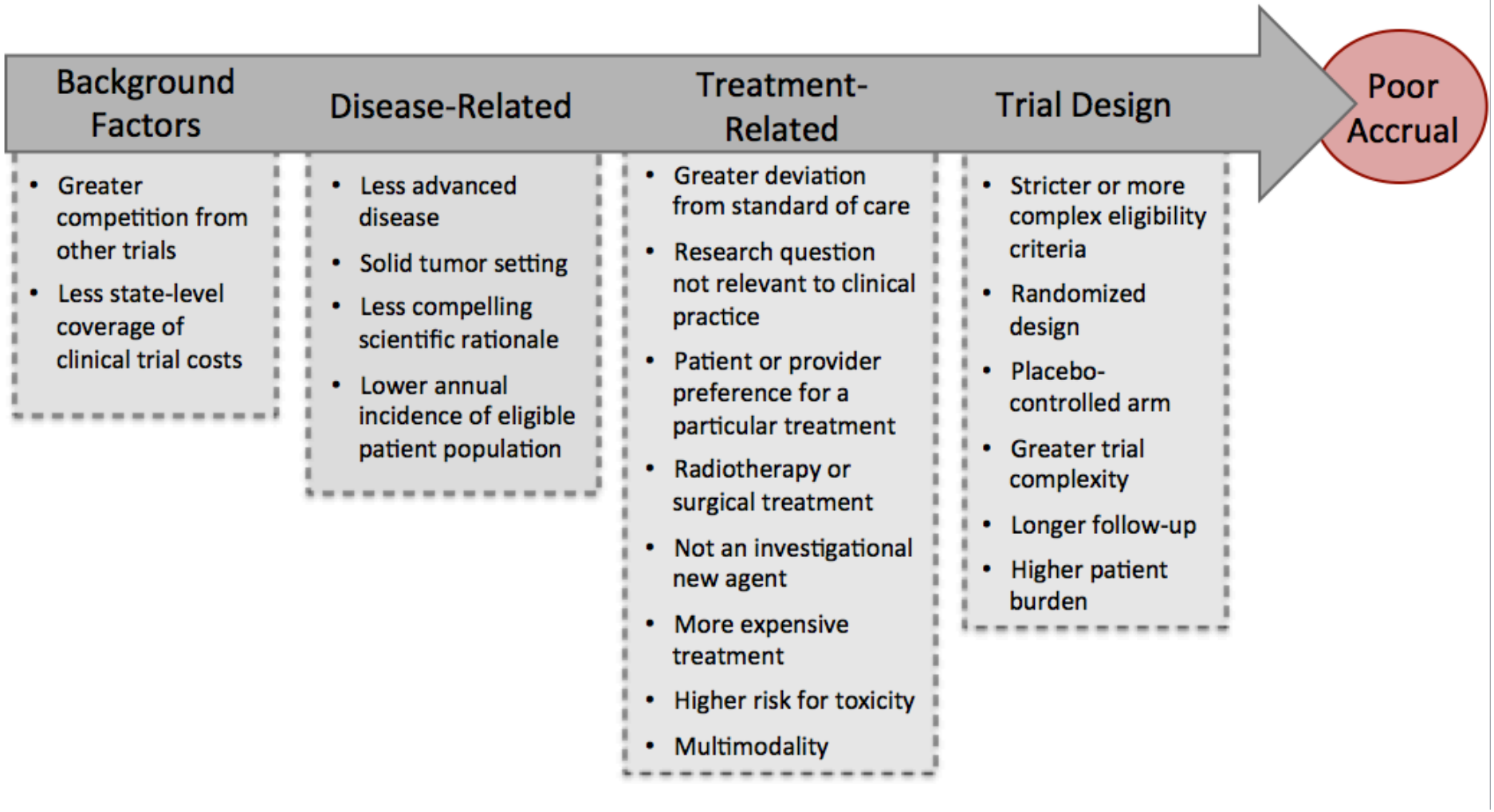
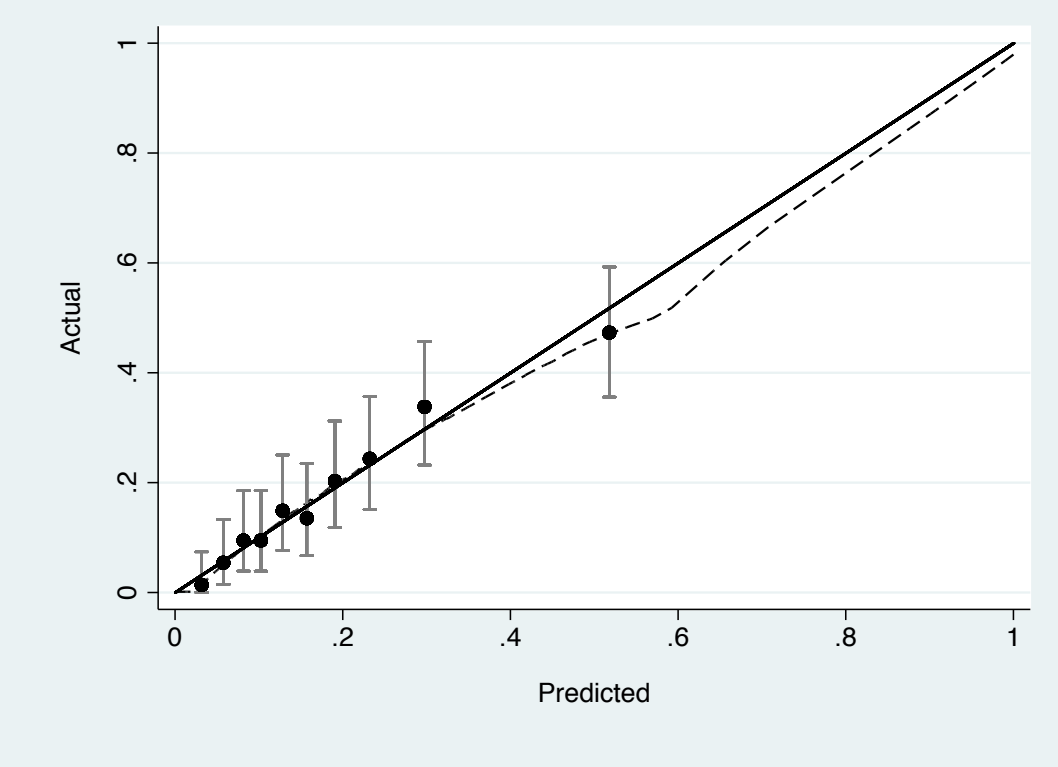


Figure 2. Calibration plot of predicted versus observed risk of poor accrual among NCTN-sponsored trials registered in ClinicalTrials.gov and started between 2000 and 2011.



Chapter II

Minimal Modeling Value of Information Analyses for Real-Time Prioritization Decisions Within a Large Cancer Clinical Trials Cooperative Group

Caroline S Bennette, David L Veenstra, Anirban Basu, Scott D Ramsey, Josh J Carlson

Abstract

Introduction: Cancer clinical trials groups face excess demand for limited research funds and patient populations. The Institute of Medicine recently highlighted the need for more systematic approaches to prioritize the selection of cooperative group-sponsored cancer clinical trials. Value of Information (VOI) analyses are an emerging methodology that can help align investments with areas in which research could have the greatest impact on patient outcomes. Though promising, many questions remain about how VOI techniques could be adapted and implemented for real world research prioritization decisions. The objective of this study was to develop and assess a pragmatic process for calculating VOI using a novel modeling approach - minimal modeling VOI, for trial proposals from SWOG, a large US-based cancer clinical trials cooperative group.

Methods: We assessed the feasibility of using a minimal modeling framework using a sample of nine randomized phase II or III trial proposals from the Breast, Gastrointestinal, and Genitourinary cancer committees that were reviewed by SWOG's leadership between 2008-2013. To engage SWOG members and customize the VOI analyses to their needs and preferences, we used a participatory model in which there was bidirectional communication among key stakeholders and the research team.

Results: The research team and SWOG stakeholders determined that a minimal modeling VOI framework that leveraged information included in the trial proposal sufficiently captured the key expected differences in comprehensive outcomes, and attendant uncertainty therein, between treatment alternatives for 8 of 9 trial proposals in our sample. Once the basic modeling framework was developed, the construction of these limited models and calculation of VOI took less than one week per trial proposal and will be feasible to conduct in real-time. To accommodate stakeholder input on the types of information and modes of presentation they found most useful, we a) deconstructed traditional VOI metrics into the expected health benefits and incremental healthcare costs associated with acquiring additional information, b) assumed within our VOI modeling framework that treatment decisions would be made on the basis of expected health benefits, and c) provided results at the individual patient and population level.

Conclusions: Setting priorities for future medical research is a complex and difficult process, but an increasingly important one given limited research resources. We developed an efficient, quantitative process for informing clinical trial prioritization that is transparent and acceptable to stakeholders. Prospective use and assessment of this approach is needed.

Introduction

Setting priorities for future medical research is a crucial but complex and difficult process. Value of Information (VOI) analyses have received increasing attention as a framework to inform research prioritization(1-5). In the first published example of using VOI methods to inform research prioritization in the US, the analyses were shown to influence the priority rankings of research topics across a range of cancer genomic applications(1). Following the success of this work and in response to national calls for improved research prioritization within cancer clinical trials cooperative groups(6), we sought to develop and integrate an efficient VOI research prioritization process into the trial proposal evaluation processes of SWOG, a large clinical trials consortium group, to provide decision makers with an additional tool to aid in the allocation of their limited research resources.

A critical step towards this objective is to develop a rapid and reproducible process for calculating VOI that is acceptable and useful to decision makers. Though our earlier efforts to implement VOI into research prioritization decisions were impactful, they were time and resource intensive and therefore not suitable for integration into real-time trial evaluation processes(1).

Our objective was to work with key stakeholders in SWOG and adapt a novel modeling approach - minimal modeling VOI – to develop an efficient and pragmatic process for calculating VOI. Herein we describe the development of this process and provide a preliminary assessment of its feasibility, strengths, and weaknesses across a retrospective sample of trial proposals. Our findings contribute to the growing literature on developing and implementing quantitative approaches to inform prioritization decisions within publicly funded research organizations.

Methods

Setting

This work was conducted as part of a Patient-Centered Outcomes Research Institute funded project evaluating a structured approach to prioritizing cancer research using stakeholders and VOI within SWOG. SWOG maintains a diverse portfolio of clinical trials across the cancer care spectrum from prevention and early detection to palliative care and quality of life for cancer survivors(7). Within SWOG, research study ideas are typically proposed and developed members from a disease committee and, if reviewed favorably by the entire disease committee, are submitted to SWOG's Executive

Review Committee (ERC) for a final internal review. Proposals reviewed favorably by the ERC are then submitted to a steering committee comprised of members from all cooperative groups and then to the National Cancer Institute's Cancer Therapy Evaluation Program for final approval or rejection. Our analyses are limited to the evaluation to proposals from the Breast, Genitourinary (GU), or Gastrointestinal (GI) disease committees, the three largest and most active disease committees within SWOG.

Overall approach

Our initial approach was primarily informed by the literature on applications and methodological approaches to VOI, particularly in the context of resource prioritization(1, 2, 5, 8) and by the conceptualization of minimal modeling*(4, 9)*. As we continued to refine our process and incorporate several rounds of stakeholder feedback regarding the type of information and modes of presentation they would find most compelling, we moved away from the VOI approaches and presentation styles typical in academic journals and towards a more pragmatic framework that is both efficient to calculate and validate with clinical experts and is acceptable to SWOG decision makers.

Study Sample

We obtained a copy of all (n=34) randomized phase II or phase III trial proposals from one of these disease committees that were reviewed by SWOG's ERC between 2008 and 2013. A member of our study team who was not involved in the VOI analyses randomly selected from among this set two approved and two rejected proposals from the Breast and GI committees and two approved from the GU committee that we used to develop our modeling approach. We planned to select two rejected capsules from the GU committee, but there were none available that met our inclusion criteria. Upon initial review of this sample, we identified one proposal (not approved) that did not fit within our pre-specified inclusion criteria for a randomized design to compare two or more interventions. Although the proposal was listed as a randomized phase II study, it did not include an alternative hypothesis in favor of one treatment, but rather in favor of both treatments relative to a historical control. In this sense the trial design represents two overlapping single arm studies, and was therefore excluded from our VOI process development. The remaining trial proposals spanned clinical settings and treatments,

ranging from the use of novel biomarkers to determine chemotherapy regimens to the evaluation of different surgical techniques.

Value of Information (VOI) Calculations

We estimated the clinical and economic value of the information that would be provided by each of the proposed trials in our sample portfolio using Bayesian updating methods(10). In brief, we created decision models for the treatment intervention(s) evaluated in each trial proposal and characterized the uncertainty around all uncertain model inputs with probability distributions. All decision models were constructed under a 'veil of ignorance' for evidence available after the trial was originally reviewed. We simulated the distribution of expected trial results according to these probability distributions and the planned sample size and length of follow up. We synthesized the existing (prior) evidence with the simulated trial results by characterizing uncertainty in existing evidence using distributions that were conjugate to the likelihood of the simulated trial data(10). We then compared the clinical and economic outcomes of decisions made with the additional evidence from the proposed trial to those made with only current evidence.

Population-level VOI measures were calculated as the per patient VOI multiplied by the size of the affected population expected to face the treatment decision being investigated by the trial over the expected lifetime of the information. The size of the affected population was derived from the Surveillance, Epidemiology, and End Results (SEER) database and published literature. We assumed a bounded 10-year time horizon for the information being generated by each trial(11, 12), with a 3% discount rate and a delay in the acquisition of information corresponding to the accrual and follow up time required by the trial(13). All analyses were performed in RStudio (RStudio, Inc., Boston, MA).

Stakeholder Engagement & Analysis

We defined stakeholders as SWOG members whose acceptance and cooperation with the VOI modeling processes and results will be essential for the prospective implementation and/or members who have a vested interest in the outcomes of this work(14, 15). We engaged a range of SWOG members (approximately 200) in an iterative and multifaceted manner to actively solicit their preferences and needs (Figure 1). Our goals were to create shared understanding of VOI analyses and to make

relevant, transparent, and effective decisions regarding its future use in SWOG's proposal evaluation process. To increase familiarity with VOI concepts, we also distributed written educational materials and provided access to online training that covered VOI techniques, interpretation, and applications (see Appendix) to all members of SWOG's Breast, GU or GI committees prior to each of our in-person meetings or web-enabled conference calls.

We used a participatory model to obtain stakeholder input in which there was bidirectional communication among SWOG members and the research team(15). Complete details about the engagement activities are included in the Appendix. In brief, we conducted an in-person VOI training session during the Spring 2014 SWOG meeting, participated in three web-enabled conference calls with SWOG ERC members, validated key inputs of all models with the chairs of each disease committee, and presented the final VOI process and results of the retrospective analysis to each of the disease committee members during the Fall 2014 SWOG meeting (approximately 150 members total). Stakeholders were asked specifically to comment on key assumptions or perceived barriers to generating or communicating VOI results that were identified *a priori* by the modeling team, but were encouraged to ask questions or discuss any other concerns or priorities that they felt were important. Field notes from each stakeholder engagement session were reviewed and annotated with summarizing comments; the resulting notes were analyzed using a targeted thematic analysis(16).

Results

The nine trial proposals used to develop and evaluate our VOI modeling approach are summarized in Table 1 and the corresponding VOI results are shown in Table 2. Three trial proposals used overall survival as the primary endpoint, four used progression-free survival, and two used recurrence-free survival. The median sample size was 680 (range: 92-3400).

Implementing a Limited Modeling Framework

Our initial intention was to sample directly from distributions representing uncertainty in comprehensive outcome measures for each intervention evaluated, following a minimal modeling approach*(4, 9);* however, six of the nine trial proposals used an intermediate endpoint, such as progression-free survival or disease-free survival, and did not report a mapping function to comprehensive endpoints.

Furthermore, for five trial proposals, the endpoints were expected to occur over a time frame of more than five years, necessitating the need to account for age-specific competing causes of death.

We therefore developed a Markov model framework that maintains a minimal modeling conceptualization by focusing on the trial's primary endpoint and consisting of up to three health states (Figure 2): (i) alive, pre-primary endpoint, (ii) alive, post-primary endpoint, and (iii) death. We derived the transition probabilities of experiencing the trial's primary endpoint for the standard or reference treatment from the relevant survival parameters included in the sample size calculations by assuming a constant failure rate (i.e. an exponential distribution) following the assumptions used in the sample size calculations. Determining the transition probabilities for the new or experimental treatment, and in particular the attendant uncertainty, is more complex and is described in the next section.

We extrapolated from intermediate endpoints to death for six trial proposals using data derived from meta-analyses that summarized the empirical relationship between surrogate endpoints and death in the respective disease setting (see Appendix for further details and examples). Lastly, we focused on cost and utility estimates that were appropriate for more broadly defined health states, such as the annual net costs of ongoing cancer treatment for a specific disease setting(17).

Characterizing the Prior Distribution of Treatment Effect

We originally hoped that trial proposals would contain sufficient data from earlier phase studies to derive an empirical prior distribution of the treatment effect; however, no trial capsules included directly translatable prior evidence (e.g. an earlier phase study of the same treatment[s] in the same clinical setting) or used meta-analytic techniques to comprehensively summarize the current evidence and its attendant uncertainty. We therefore concurrently developed a pragmatic approach to incorporate formal expert elicitation of SWOG members into our prospective process and a suitable alternative for the retrospective review of trial proposals.

Both the planned prospective and retrospective approaches leverage the evidence synthesis and implicit expert opinion used in the trial's sample size calculations. The retrospective VOI analyses relied on the historical success rate of past cooperative group cancer trials. Specifically, just over half of late phase cooperative group clinical trials found new treatments to be at least marginally better than existing or

standard treatments and approximately one-quarter found a statistically significant result in favor of the new treatment(18). For the retrospective proposals, we therefore aligned the prior distributions of treatment effects such that the probability of observing a treatment effect equal or better than that under the alternative hypothesis 0.25 and the probability the treatment effect was equal or better than that under the alternative hypothesis was 0.60. These estimates were considered appropriate for each trial in our sample by the chairs of each disease committee, and were generally accepted as reasonable starting points by SWOG stakeholders more generally. Using the expected values under the null and alternative hypotheses used in the sample size calculations as anchors we then construct a prior distribution of the treatment effect estimate for the trial's primary endpoint (see the Appendix for a worked example).

Establishing the Probability of Effectiveness Required to Change Clinical Practice

The majority opinion of SWOG members and frequent treatment adoption decisions in the United States are made on the basis of expected health benefits alone, rather than expected net benefits. We therefore mirrored this decision to adopt or reject a new treatment based on health benefits alone within our simulation framework. Furthermore, to account for the risk aversion associated with adopting new interventions, albeit implicitly, we established a minimum probability the new intervention was more effective that was required to change clinical practice. This was chosen to be 80% for the retrospective analyses, roughly corresponding to the upper bound of clinical equipoise, and a point beyond which SWOG members felt a trial would no longer be warranted or ethical to establish the effectiveness of a new treatment. Different thresholds [side note: and/or approaches – still like idea of using minimal clinical difference in primary endpoint – easy for stakeholder to understand?] may be used in the prospective evaluation depending on the perceived risk-benefit of a new treatment.

Feasibility of Applying a Minimal Modeling VOI Framework

We determined the limited modeling framework was not appropriate for one trial proposal to evaluate interventions expected to have important differences in quality of life that would affect treatment decisions, but which only included overall survival as a primary endpoint and because there was no appropriate mapping function from overall survival to quality-adjusted life expectancy in this setting (Proposal I).

Based on background information presented in the trial proposal, the trial's design and stated purpose, and informal discussions with clinical experts, the modeling team initially determined that a limited modeling framework could be applied to 8 of the remaining 9 proposals included in our sample. Our criteria for determining modeling feasibility were that the model captured the key expected differences in comprehensive outcomes either directly via the treatments' impact on the primary endpoint (n=2) with adjustment for quality of life impacts or indirectly if a mapping function existed to link the surrogate endpoint to comprehensive outcomes (n=6).

After reviewing each of the models for their respective committee, the chairs of each disease committee confirmed that our limited modeling framework was acceptable, informative, and sufficiently captured the key expected differences in outcomes between the treatments under study in these 8 proposals.

The construction and calculation of limited modeling VOI estimates took one researcher approximately four to five hours per trial proposal once the final process was developed. Despite the limited number of modeling inputs required, the majority of this time was spent reviewing the literature for appropriate values and validating these with clinical experts and other stakeholders. Although a roughly one week turnaround time for generating VOI estimates will fit within the current timeline of SWOG's ERC, we are also working with SWOG to further reduce the time required by asking that key modeling inputs be included in all future trial proposal submissions.

Aligning VOI Metrics with Stakeholder Preferences

The feedback we received from SWOG members led us to deconstruct the clinical and economic components of VOI in both our calculations and communication of results. A slight majority of SWOG members expressed the sentiment that SWOG's mission was to conduct trials that had the greatest potential impact of improving health regardless of costs (*"You can't say an improvement in survival is a negative because of costs. It's matter of philosophical differences between clinicians and health economists.")*. Others felt that drug prices were ultimately out of SWOG's control and were often difficult or impossible to know before a trial started, particularly for new investigational agents without a market price.

A slightly smaller group of SWOG members directly countered these statements by arguing that ignoring costs would be "naïve and shortsighted" given the extremely high cost often associated with improvements in cancer treatment. They felt that the

costs of many cancer therapies had reached a tipping point, and that it was critical for SWOG to start considering how their clinical trial investments could alleviate or aggravate this problem. Other members pointed out that some trials, particularly those in early stage cancers, were evaluating interventions to prevent progression and that a key secondary benefit of reduced progression would often be reduced downstream medical costs (*"What if you were saving costs? Some trials in early stage bladder cancer would do just that…it would reduce downstream medical costs"*).

To accommodate these divergent stakeholder preferences regarding treatment costs, as well as mirror the usual treatment adoption decisions in the US, the decision to adopt or reject a treatment without our simulation framework is made on the basis of health benefits alone. Furthermore, we report the expected incremental health benefits and incremental healthcare costs associated with acquiring additional information from a clinical trial separately.

Lastly, several SWOG members who studied rare cancer conditions expressed concerns that population-level VOI estimates would provide an unfair measure of value for trials in rare cancers *("If you compare all the trials in pancreatic cancer versus all the trials in breast cancer, you'll of course find higher VOI in breast cancer"*) and were unclear how population-level estimates would align with SWOG's mission to pursue trials that less likely to be pursued by industry or single institutions, particularly those in rare cancers. To accommodate these concerns and preferences, we therefore report both individual-level and population-level VOI measures for each trial proposal.

Decision Makers' Acceptance of VOI Analyses to Inform Research Prioritization

We received generally positive feedback from SWOG members when we presented the final modeling process and results of our retrospective VOI analysis. In particular, members expressed enthusiasm and support for the idea of using VOI analyses to inform trial prioritization decisions *("What they're doing is incredibly important… You will see trials with negatives. We need it to make strategic decisions" – GU member*).

SWOG members also stated that the process of calculating VOI would be a useful and informative exercise in itself by requiring members to be explicit about the likelihood of a trial reaching its endpoint *("We don't do this often enough. We're not critical enough to ask directly, 'what is the likelihood of reaching the trial's endpoint?'"*) or the assumptions used in sample size calculations *("This method [VOI] ties us more*

closely to the assumptions [the statistician] is going to make in the sample size calculations"). SWOG Executive members felt that formal elicitation of the disease committee regarding the likelihood of a trial's result being strong as under the alternative hypothesis would be particularly useful for their triage decisions.

Final VOI modeling and communication process

Our final process for calculating VOI for SWOG's trial proposals is outlined in Figure 1. It involves building an initial model based on the information included in the trial proposal. When available, the uncertainty in treatment effects are derived from the prior evidence included in the proposal; when not available, we employ a simple expert elicitation exercise. We then verify this model with clinical experts from the respective disease committee, create a final model, and determine which results will be generated based on stakeholder preferences and availability of data: incremental benefits only in the case of most therapies without a current market price or when there are other stakeholder concerns regarding inclusion of healthcare costs; otherwise incremental benefits and healthcare costs are reported. Lastly, an overarching component of the process is the training of SWOG members in VOI concepts and applications. The majority of this training was conducted during the development of the VOI modeling process and retrospective analysis, although it will continue as needed during the prospective evaluation.

Discussion

Summary

We worked with key stakeholders to develop an efficient and customized VOI modeling framework that will be implemented prospectively into SWOG's trial proposal evaluation processes. Our limited modeling VOI process focuses on the primary endpoint of the proposed trial, leverages the prior evidence summarized in the proposal, and when necessary involves a simple and pragmatic approach to elicit expert opinion regarding prior uncertainty in treatment effectiveness. We also modified the calculation and presentation of VOI results to more closely align with SWOG stakeholder preferences.

Implications

We found that with some modifications limited modeling VOI analyses were feasible for 8 of 9 trial proposals in our sample. Furthermore, the reason why calculating VOI was not feasible for the remaining proposal was nevertheless informative of the trial's expected value: a trial in which the primary endpoint does not capture key expected differences in patient outcomes is unlikely to generate valuable evidence to inform treatment decisions. It is therefore telling that this proposal was not approved by SWOG. This finding also highlights a larger theme that emerged from presenting our VOI modeling process and results to stakeholders: in many cases the explicit process of creating decision models and characterizing current uncertainty was as informative as the VOI results in understanding a trial's expected value.

The methods and processes described herein are the basis for prospective processes that are currently underway within SWOG. The only difference in our prospective calculations is that when we calculate VOI for future trial proposals we will either use available prior data (preferred but rarely available) or formally elicit from members of the respective disease committee the likelihood of observing an outcome consistent with the null or alternative hypothesis. The historical rate of trial success will serve as a benchmark for these expert elicitation exercises.

We worked in collaboration with SWOG stakeholders to customize both the calculation and presentation of VOI results to improve the acceptance of VOI analyses and their usefulness in complimenting other SWOG priorities when evaluating future trial proposals. For example, a key mission of SWOG is to pursue trials that less likely to be pursued by industry or single institutions, and decision makers in SWOG view trials in rare cancers as aligning strongly with that mission. SWOG decision makers therefore place an higher value, albeit implicitly, on trials in rarer cancers that is not directly reflected in the population level VOI estimates. In this framework, the decision makers' preferences for rare cancers can remain implicit, but the opportunity costs of such preferences are made explicit.

Our results can also be used to guide future efforts to implement VOI analyses into research prioritization decision-making at other organizations or agencies. In particular, we recommend (i) providing repeated exposure to VOI concepts, ideally in different formats to accommodate a range of preferences for learning and engagement styles (e.g. printed materials, in-person presentations, web-based training), (ii) presenting concrete and tangible examples of VOI analyses for research studies with which decision makers are already familiar, (iii) using an open forum or other avenue for

stakeholders to ask questions and express their concerns before the analytical approach is finalized or implemented, and (iv) provide multiple options and metrics for receiving the results.

Comparison with other studies

Carlson *et al.* used VOI analyses to help decision makers identify and prioritize future research areas in cancer genomics(1). The approach described here differs importantly from this work by conducting VOI analyses on trial proposals that have already been developed rather than broadly defined research topics. The major advantage of this approach is efficiency. By capitalizing on the considerable work that goes into developing a trial proposal and limiting our model to the narrowly defined clinical question being proposed, we can calculate VOI efficiently and in a manner that is consistent with real-time evaluation of trial proposals.

It was also efficient to validate key inputs and assumptions with stakeholders given their familiarity with the trial proposals and the limited number of modeling inputs used. The validation process took less than ten minutes per trial proposal; however, this step occurred several months after the initial models were developed. Establishing a consistent and ongoing interface between the modeling team and key clinical stakeholders will be critical to ensure these models are built and validated quickly when VOI analyses are implemented prospectively into SWOG's proposal evaluation processes.

PCORI recently commissioned a white paper on the potential use of VOI techniques to inform research prioritization decisions in the United States(19). Though we did not base our process on the methods described in this report, we nevertheless arrived at similar conclusions in many respects. Analogous to the approach taken in the PCORI report, we focused on the clinical benefits of acquiring information; however, unlike in the PCORI report, we also reported as a separate measure the expected incremental healthcare costs of acquiring additional information when future treatment decisions would be made based on clinical benefits alone. In other words, some SWOG decision makers may choose to prioritize trial investments based on net (rather than clinical) benefit, but must do so within a framework in which treatment decisions will still be determined by clinical benefits.

Claxton and Sculpher conducted a pilot study using VOI analyses to inform research prioritization decisions within the UK(20). Their primary challenges were not

technical or methodological, but the reluctance of decision makers to adopt explicit criteria for research prioritization. We anticipated that SWOG members would be similarly reluctant to consider VOI analyses in setting research priorities; however, we found that they all understood the implications of the organization's diminishing research budget and were generally enthusiastic and interested in quantitative tools that could inform their investment decisions. The key point of disagreement was the extent to which SWOG was responsible for considering costs of cancer treatment when developing or prioritizing clinical trials. Though our final VOI modeling process will not provide a definitive answer to this question, it will in many cases make the opportunity costs to society of not considering downstream healthcare costs explicit. The extent to which this information ultimately influences decision makers and leads to more efficient use of scarce resources remains to be evaluated.

Limitations

There are several key limitations to this work that warrant discussion. First, we did not conduct a formal survey of SWOG stakeholders' opinions of the VOI methods or results. Our objective was to identify key barriers to using VOI analyses to inform SWOG's investment decisions and refine our modeling approach accordingly. To do so, we engaged directly with SWOG members through various formats and at various times, thereby providing multiple opportunities for different voices to be heard and provide feedback. We received positive feedback from the ERC and the Breast, Gastrointestinal and Genitourinary Disease Committees and are proceeding with the prospective evaluation; we are therefore confident that the majority of stakeholders accept our final VOI modeling process.

The second limitation to these analyses is the relatively small sample of trial proposals used in developing our approach. It is possible that a larger sample of proposals could have resulted in a slightly different final VOI modeling process or conclusions regarding feasibility; however, generating VOI estimates for a larger sample was not possible within the tight timelines we were operating under to begin the prospective evaluation. The prospective evaluation will therefore serve as an important continuation of the VOI process development and feasibility assessment as well as providing critical information on how VOI analyses influence proposal evaluations.

Our limited modeling VOI process also has several potential drawbacks. First, our decision models may be overly simplistic representations of complex clinical

processes. Though the chairs of each disease committee confirmed that our limited models sufficiently captured the key outcomes of the treatment decision in the sample of historical trial proposals, it will be important to determine whether additional modifications or refinements to our process are necessary when implemented prospectively and across a larger sample of trial proposals.

Second, our VOI modeling process relies on the assumption that the clinical trial proposals are scientifically and clinically appropriate. The VOI results will be incorrect and potentially misleading if a trial proposal mischaracterizes the current body of evidence regarding the effectiveness of an intervention. Furthermore, a key assumption of our modeling framework is that the comparator arm represents current standard of care. Feedback from SWOG stakeholders indicated that this assumption was appropriate for all of the trial proposals in our sample, but it may not be generalizable to trials that compare two or more interventions that are both being widely used. If such a situation is encountered in the prospective VOI evaluation, we will need to carefully distinguish between the value of information potentially generated from the trial and the value of implementing currently available evidence into clinical practice(21, 22).

Conclusions

We developed an efficient and reproducible process to rapidly generate VOI estimates for cancer clinical trial proposals that is transparent and acceptable to decision makers and stakeholders within SWOG. Our findings indicate that implementing limited modeling VOI analyses within a clinical trials research organization's real time proposal evaluation processes is generally feasible and acceptable to stakeholders with appropriate customization. Future work will assess whether this approach to calculating VOI can meaningfully inform and ultimately influence prospective clinical trial research investment decisions within SWOG and thereby help align their research portfolios to have the greatest public health impact.

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Table 1. Summary of 9 trial proposals reviewed by SWOG's Executive Review Committee between 2008 and 2013 that were used to develop our VOI analyses processes.

Proposal ID	Official Title	Phase	Sample Size	Committee	Endpoint	Year Reviewed
A	Prospective Evaluation Of The Benefit Of A Standard Versus An Extended Pelvic Lymphadenectomy Performed At Time Of Radical Cystectomy For Bladder Cancer With Adjuvant Chemotherapy Administration For Node Positive Disease	III	630	GU	PFS	2010
B	A Phase III Randomized Trial Comparing LHRHa + TAK-700 with LHRHa + Bicalutamide in Patients with Newly Diagnosed D2 Prostate Cancer	III	1486	GU	OS	2011
C	A Randomized Phase II Pilot Study Prospectively Assigning Treatment for Patients Based on ERCC1 for Advanced/Metastatic Gastric Cancer or Gastroesophageal (GE) Junction Cancer	II	200	GI	PFS	2010
D	Randomized Phase II Clinical Trial of AZD-6244 and MK-2206 vs mFOLFOX in Patients with Metastatic Pancreatic Cancer after Prior Chemotherapy	II	120	GI	OS	2011
E	Randomized Phase II study comparing the novel MEK inhibitor, trametinib, to standard of care chemotherapy in patients with KRAS mutant metastatic colorectal cancer	II	92	GI	PFS	2013
F	Exemestane vs. a Combination of Exemestane and the Monoclonal Antibody IGF-1R Inhibitor IMC-A12 in Patients with Metastatic ER/PgR Positive Breast Cancer	III	690	Breast	PFS	2009
G	Capecitabine and Dasatinib as Adjuvant Therapy in Patients with HER-2/neu Negative Breast Cancer	III	720	Breast	RFS	2008
H	Adjuvant endocrine therapy +/- everolimus in patients with high-risk, node-positive, hormone receptor positive and HER2-neu normal breast cancer	III	3400	Breast	RFS	2011
I	Intensive vs. Less Intensive Dosing of Zoledronic Acid vs. Denosumab as Adjuvant Therapy for Early Stage Breast Cancer	III	680	Breast	OS	2010

PFS=Progression-free survival; OS=Overall survival; RFS=Recurrence-free survival
GU=Genitourinary; GI=Gastrointestinal

Table 2. Per-patient and population-level VOI metrics for 9 retrospective trial proposals. Expected clinical benefits of acquiring additional information monetized at a willingness to pay of $100,000 per QALY ("clinical VOI") and expected incremental healthcare costs are shown separately; see Methods section for more details.

	Per-Patient		Population-level	
Proposal ID	Clinical VOI	VOI	Clinical VOI	VOI
A	$43,800	$42,000	$3,300,000,000	$3,100,000,000
B	$14,700	-$77,300	$1,000,000,000	-$4,222,364,596
C	$9,200	-$23,000	$490,000,000	-$1,210,000,000
D	$16,000	-$14,476	$2,100,000,000	-$1,900,000,000
E	$9,400	-$6,400	$1,100,000,000	-$700,000,000
F	$48,100	-$5,900	$6,600,000,000	-$700,000,000
G	$25,800	$2,600	$4,300,000,000	$400,000,000
H	$30,200	$5,400	$2,100,000,000	$400,000,000
I	n/a	n/a	n/a	n/a

Figure 1. Overview of VOI modeling process and engagement with SWOG members.

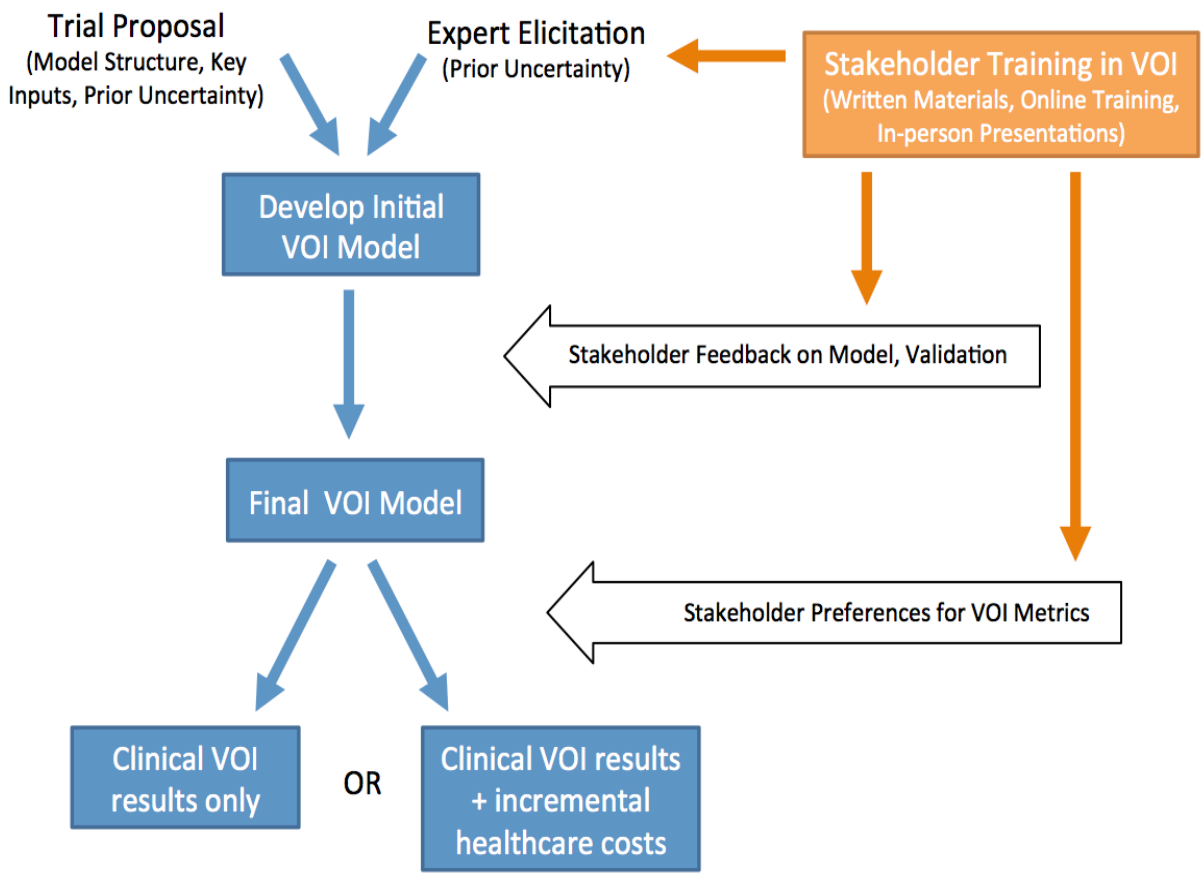
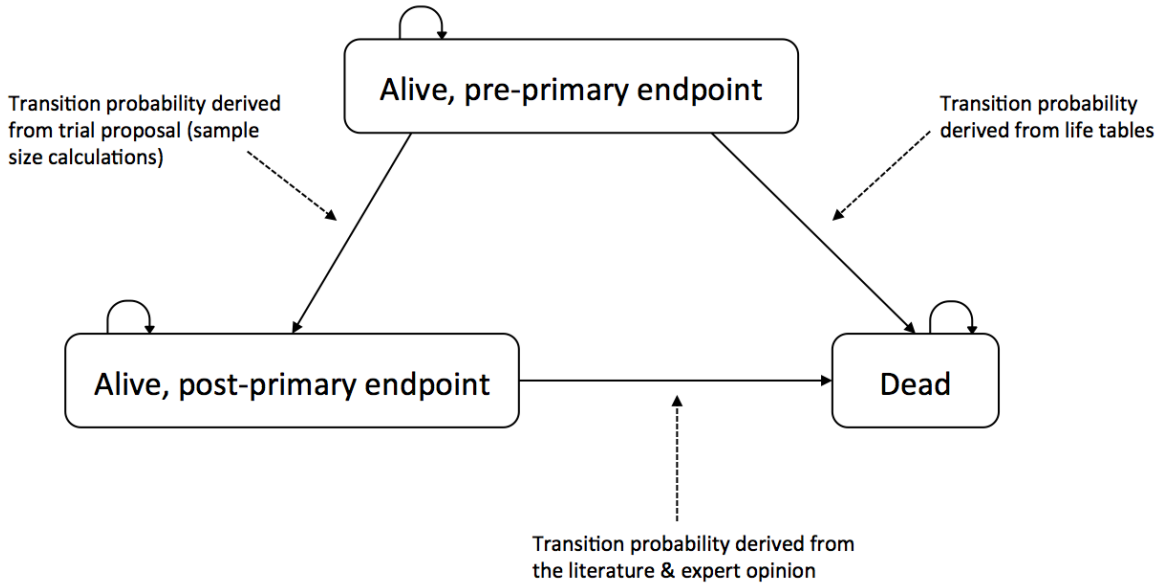


Figure 2. Depiction of the Markov modeling framework used in our VOI calculations. When the primary endpoint of the trial is overall survival, the health states for alive, post-primary endpoint and dead are collapsed into a single state.



Chapter III

Optimizing cancer clinical trials research investment decisions in the US: a proof of concept portfolio evaluation

Caroline S Bennette, Joshua A Roth, Anirban Basu, Josh J Carlson, Scott D Ramsey, David L Veenstra

Abstract

Background: A major challenge the National Clinical Trials Network (NCTN) faces is the selection and prioritization of trial concepts with the goal of improving patient care. The Institute of Medicine recently stressed that rigorous prioritization of trial concepts was a critical goal to ensure that limited public funds are used effectively. Yet despite ardent calls to improve the means of prioritizing and selecting cancer clinical trials, many questions remain about how to achieve these goals.

Methods: We applied a proof of concept portfolio evaluation to a historical sample of nine randomized phase II/III clinical trial concepts reviewed by a large clinical trials cooperative group, SWOG, between 2008 and 2013. Five of these trial concepts were ultimately approved and four were not. Risk was defined as the probability of achieving sufficient accrual (>50% of target). Societal return was defined in terms of expected health benefits (clinical return) or net benefits (net return) using Value of Information analyses. We compared the risk-adjusted expected returns of the current portfolio of approved trials to hypothetical alternative portfolios identified using an integer programming optimization model with total planned patient enrollment as the primary constraint.

Results: The clinical return of SWOG's sample portfolio was $11.3 billion. An alternative hypothetical portfolio of trial concepts that required approximately 200 fewer patients total than the current portfolio was expected to have a clinical return of $26.3 billion. The net return of SWOG's current portfolio was $2.7 billion. An alternative hypothetical portfolio of four trial concepts that required 400 fewer patients than the current portfolio was expected to have a net economic return of approximately $9.6 billion. Lastly, selecting a portfolio of trials to maximize clinical return would increase the net return by $7 billion.

Limitations: Other criteria may influence trial concept approval and funding decisions and limit potential gains in efficiency. Very small sample of trial concepts included in this proof of concept analysis. Gains in efficiency seen on retrospective evaluation may not be attainable in real-time or prospective investment decisions.

Conclusions: We found that a portfolio evaluation is a feasible and potentially useful response to the IOM's call for more systematic approaches to select and prioritize trial concepts against one another. The approach can facilitate the ranking of a large

number of trial concepts simultaneously using two key criteria – expected accrual feasibility and societal return – and also inform longer-term strategic decision-making. A portfolio evaluation approach could therefore help NCTN decision makers select and prioritize trial concepts that have the greatest potential to improve population health and thereby optimize the return on limited research funds.

Introduction

Randomized clinical trials are pivotal in generating evidence to inform medical and health policy decisions, but are extremely costly and time consuming to plan and conduct - a large, phase III trial often costs upwards of several hundred million dollars and takes decades to complete (1). Faced with limited budgets, organizations that support and fund clinical trials must select and prioritize the most promising trials; however, the best methodological approaches to explicitly and systematically prioritize public funding of medical research are only beginning to be thoroughly explored and evaluated.

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) stressed 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 to the current review process, the IOM report did not endorse or recommend any specific strategies for implementing this rigorous and systematic prioritization approach.

Setting priorities for future research is a complex process that has received considerable recent interest(7-9). Portfolio management is a popular method to prioritize investments within the financial sector as well as many industries, including

pharmaceutical companies(10). Yet despite the conceptual simplicity and appeal of using these approaches to prioritize and manage the NCTN portfolio, it is difficult to define appropriate measures of risk and return for the publicly funded trials. In our previous work we developed novel methods to measure the risk and return of NCTN-sponsored trials.

In this paper, we apply a 'proof of concept' portfolio management approach to the historical portfolio of trial concepts reviewed by a large clinical trials cooperative group, SWOG, and in so doing illuminate how such an approach could improve the efficiency and transparency of clinical trial approval decisions. This analysis was conceived and conducted in direct response to the IOM's call for efforts to rigorously prioritize the selection and support of publicly funded cancer clinical trials. Our primary objectives were to determine if this type of analysis was feasible and to provide a preliminary assessment as to whether quantitative measures of risk and return could theoretically improve the efficiency of SWOG's research portfolio.

Methods

Study Sample

We obtained a copy of all (n=34) randomized phase II or phase III trial proposals from one of these disease committees that were reviewed by SWOG's Executive Review Committee between 2008 and 2013. A member of our study team who was not involved in these analyses randomly selected from among this set two approved and two rejected proposals from the Breast and GI committees and two approved from the GU committee that we used to develop our modeling approach. We planned to select two rejected capsules from the GU committee, but there were none available that met our inclusion criteria. Upon initial review of this sample, we identified one proposal (not approved) that did not fit within our pre-specified inclusion criteria and was therefore excluded from these analyses. The remaining nine trial proposals spanned clinical settings and treatments, ranging from the use of novel biomarkers to determine chemotherapy regimens to the evaluation of different surgical techniques (Table 1).

Estimating risk and return

We estimated the risk of poor accrual for each trial proposal in our sample using a previously developed and validated prediction model. Full details about the development and validation of this model are included in Chapter I. In brief, we used a training set of phase II/III adult NCTN-sponsored trials that opened between 2000 and

2011 to develop a model to predict poor accrual, defined as trials that closed with only or were currently accruing at <50% of target. Candidate risk factors were identified from a literature review and interviews with clinical trials experts and the model was externally validated using trials opened in 2012 and 2013.

We estimated the net present value for each trial proposal using value of information (VOI) techniques. VOI analyses are a systematic and quantitative approach to estimate the societal benefit of acquiring additional evidence to inform a decision. VOI analyses put a value on reducing uncertainty by calculating how the costs and consequences of decisions made with future evidence might differ from those made today and can thereby help align investments with areas in which research would have the greatest potential impact on patient outcomes.

Full details about the development of the VOI analyses, which were specifically customized to SWOG stakeholders' preferences and needs, are included in Chapter II. In brief, we developed decision-analytic simulation models to project the long-term clinical and economic outcomes of the treatment decision being investigated by the proposed clinical trials, primarily using data included in the trial proposal supplemented with published literature and expert opinion. We characterized the current uncertainty around all model inputs with probability distributions. We simulated trial results according to these probability distributions and the planned sample size and length of follow up. We then synthesized the existing (prior) evidence with the simulated trial results using Bayesian updating methods. We then compared the clinical and economic outcomes of decisions made with additional future evidence from the proposed trial to those made with only current evidence, assuming that all treatment decisions would be made to optimize health benefits (i.e. regardless of costs) as long as there was at least 80% probability that the new or experimental treatment was superior to the control. We estimated the clinical value as the gain in quality-adjusted life years (QALYs) monetized at a willingness to pay threshold of $150,000 per QALY expected by acquiring additional information.

We estimated the economic value as the clinical value minus the incremental healthcare costs associated with decisions made on the basis of additional information. We then multiplied by the size of the affected population expected to face the treatment decision being investigated by the trial over the expected lifetime of the information. The size of the affected population was derived from the Surveillance, Epidemiology, and End Results (SEER) database and published literature. We assumed a bounded 10-year time horizon for the information being generated by each trial(13, 14), with a 3% discount rate and a delay in the acquisition of information corresponding to the accrual

and follow up time required by the trial(15). Lastly, we subtracted from the clinical or economic value the expected costs of the trial (assumed to be $10,000 per patient enrolled) to obtain estimates of return.

Identifying 'Optimal' Portfolios

We defined two related objective functions that we sought to maximize when identifying hypothetical alternative research portfolios: (i) risk-adjusted clinical return, and (ii) risk-adjusted net return. In both metrics, we multiplied the expected return by the probability of achieving sufficient accrual.

The primary constraint for these analyses was defined as the total number of patients enrolled in all trials in the current portfolio (n=5851), which is a proxy for the overall budget constraint. The alternative portfolios that maximized expected returns were identified with an integer programming optimziation model using a branch and bound algorithm(16). Although it may be feasible to manually enumerate each possible combination of trial proposals included in this proof of concept evaluation (there are 252 possible ways to choose 4 out of 9 trials) and then identify the optimal set of portfolios that satisfy the constraint, such calculations would grow exponentially more difficult with increasing numbers of trial proposals (e.g. choosing 10 of 20 trials would require nearly 200,000 enumerations). Furthermore, an integer programming model is concise and provides a clear and flexible framework for including additional constraints. The proof of concept optimization model, presented below, was constructed in Microsoft Excel and used the Solver Add-in to solve:

Maximize Expected Return of Portfolio: $\sum_{i=1}^{N} r_i * x_i$

Subject to:

$$\sum_{i=1}^{N} v_i * x_i \leq 5851 \text{ (i.e. total \# of patients included in current portfolio)}$$

Where:

$$x_i = \begin{cases} 1 \text{ if trial } i \text{ is selected for funding} \\ 0 \text{ otherwise} \end{cases}$$

r_i = risk-adjusted expected return (clinical or net) of trial proposal i

v_i = sample size of trial proposal i

Results

Table 2 shows the expected clinical and net returns, with and without risk adjustment, for the sample of nine proposals included in these analyses. The clinical

value was high for all trial proposals, ranging from $735 million to nearly $10 billion; however, many of the expected clinical benefits were associated with large incremental healthcare costs. Therefore the net (clinical + economic) return of the trials was considerably lower, and in some cases negative, ranging from -$3.7 billion to $4.8 billion.

The results in Table 2 also illustrate the impact that risk adjustment has on expected returns. Overall the probability of achieving >50% target accrual ranged from 0.72 to 0.98. Thus when we accounted for the trial-specific risk of poor accrual, and thereby the reduced likelihood of answering the scientific question or realizing the expected returns, we found expected returns ranged from 2 to 30% lower than without risk adjustment.

The overall risk-adjusted clinical return of SWOG's sample current portfolio of five trials was approximately $11.3 billion (Figure 1a). A hypothetical alternative portfolio of six trial concepts was expected to have a total risk-adjusted clinical return of $26.3 billion (Figure 1b), representing a greater than twofold improvement in the overall clinical return relative to the current portfolio.

Due to the high incremental healthcare costs associated with many of the expected clinical benefits, the overall risk-adjusted net return of SWOG's current portfolio was lower, approximately $2.8 billion (Figure 2a). A hypothetical alternative portfolio of four trial concepts that required 400 fewer patients had a risk-adjusted net return of $9.6 billion (Figure 2b), representing an absolute improvement on return of nearly $7 billion over the current portfolio.

Discussion

We conducted a proof of concept portfolio evaluation of a sample of trial proposals recently reviewed by SWOG, a large clinical trials cooperative group. We estimated the risk of a trial failing to reach more than half its intended target accrual and the expected societal return on investment, both in clinical and net economic terms. Our results indicated that our recently developed measures of risk and return that were targeted to NCTN-sponsored trials could facilitate a portfolio evaluation in this setting. Furthermore, our results suggest that a portfolio evaluation has the potential to improve the efficiency of research investment decisions and thereby the public health impact of limited research funds.

Implications

To our knowledge, this analysis represents the first example of adjusting expected value of information estimates to account for the risk a proposed study is

unable to answer its intended question due to accrual feasibility challenges. Risk adjustment of returns is a common practice in the financial sector and other business settings, but to date has not been applied in published VOI analyses. Without taking into consideration the risk of poor accrual or other feasibility challenges, typical VOI calculations will provide overly optimistic estimates of expected value.

The landmark IOM report that was the genesis for these analyses repeatedly emphasized that the current proposal review process should be strengthened and streamlined, and in particular that proposals should be ranked against each other. Portfolio evaluation is theoretically well suited to managing and prioritizing SWOG's and NCTN's research portfolio because the approach provides a means of efficiently summarizing both the expected accrual feasibility and societal return – two critical criteria – for a large number of trial concepts simultaneously and therefore provides a framework for evaluating trial concepts against one another.

Furthermore, portfolio evaluation is a flexible framework and could facilitate strategic decision-making, such as determining trial priorities across disease areas or considering how the portfolio should be balanced with respect to randomized Phase II or Phase III trials, as it is commonly used in other settings. With a larger sample of trial concepts or via simulation exercises, it would be possible to explore hypothetical alternative portfolios that take into account these or other measures. In this relatively simple proof of concept analysis, we found that the trial concepts included in the portfolio selected to maximize expected clinical return were simply the six trials with the highest individual returns; however, such a result is not always the case when potential research investments are non-divisible. With a larger sample of trial concepts, we might find that two or three smaller trials collectively offer a higher return than a single large trial, even if one of the smaller trials has a lower relative return on investment. Portfolio evaluation could therefore inform both individual prospective trial approvals as well as guide development of overall strategic priorities, an activity the IOM report specifically noted was currently lacking from the trial concept review process.

Claxton and Sculpher recently stated that the general reluctance to adopting transparent and explicit criteria to inform research priorities was similar to the challenges encountered when first implementing formal analyses to guide health technology assessments(17). They concluded that, "confronting decision makers with the opportunity costs of failing to consider formal analysis made some contribution to the radical change in the policy environment, at least in the UK."(17) It is our hope that this analysis [at least when expanded] will similarly require decision makers to confront the real opportunity costs of opaque and unsystematic clinical trial investment decisions.

Limitations

Some caution is warranted in interpreting the results of this analysis. The primary objective of these analyses was to establish a proof of concept rather than generate informative estimates. The sample set was purposefully limited and therefore does not provide a meaningful estimate of the value of SWOG's current research portfolio or hypothetical alternatives. These analyses do, however, establish the feasibility of using portfolio assessment to manage clinical trial research investments and provide the necessary, but not sufficient, condition to conclude this type of analysis could improve the efficiency of those investment decisions.

Another important limitation is that the potential gains in expected value seen with a portfolio assessment like this one represent an upper bound that might have been achieved if there were no additional constraints or objectives. Future work in this area could therefore focus on clarifying and potentially quantifying preferences for other objectives, such as the priority of investments in rare cancer conditions relative to more common settings, which typically have higher societal returns due to the larger number of individuals affected. An important next step is to understand what, if any, additional criteria were used when reviewing the current sample of proposals. For example, why were trial proposals G and H, which showed very high expected clinical returns and positive economic returns, nonetheless not approved?

Another key assumption of these analyses is that decision makers could have known about and made investment decisions cognizant of all potential future trial concepts in the pipeline. A prospective evaluation of how using these metrics influence trial approval decisions would therefore also be an important potential area of future investigation. It is possible that presenting decision makers with sufficient context regarding the expected returns of trial concepts relative to the current or past portfolio is sufficient to meaningful inform future clinical trial investments. For example, decision makers might choose not to commit resources to a trial concept that has lower expected return than other trials in the portfolio or another trial concept that was previously rejected on the assumption that a higher value trial will likely soon, if not already, be available.

Conclusion

Public investments in cancer clinical trials can offer substantial returns, particularly in terms of health benefits, but there are typically more potentially valuable trial concepts proposed than there are resources available to support them. Portfolio

management is a feasible response to the IOM's call for more systematic approaches to select and prioritize trial concepts that have the greatest potential to improve population health and thereby optimize the return on limited research funds.

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B	A Phase III Randomized Trial Comparing LHRHa + TAK-700 with LHRHa + Bicalutamide in Patients with Newly Diagnosed D2 Prostate Cancer	III	1486	GU
C	A Randomized Phase II Pilot Study Prospectively Assigning Treatment for Patients Based on ERCC1 for Advanced/Metastatic Gastric Cancer or Gastroesophageal (GE) Junction Cancer	II	200	GI
D	Randomized Phase II Clinical Trial of AZD-6244 and MK-2206 vs mFOLFOX in Patients with Metastatic Pancreatic Cancer after Prior Chemotherapy	II	120	GI
E	Randomized Phase II study comparing the novel MEK inhibitor, trametinib, to standard of care chemotherapy in patients with KRAS mutant metastatic colorectal cancer	II	92	GI
F	Intensive vs. Less Intensive Dosing of Zoledronic Acid vs. Denosumab as Adjuvant Therapy for Early Stage Breast Cancer	III	680	Breast
G	Exemestane vs. a Combination of Exemestane and the Monoclonal Antibody IGF-1R Inhibitor IMC-A12 in Patients with Metastatic ER/PgR Positive Breast Cancer	III	690	Breast
H	Capecitabine and Dasatinib as Adjuvant Therapy in Patients with HER-2/neu Negative Breast Cancer	III	720	Breast
I	Adjuvant endocrine therapy +/- everolimus in patients with high-risk, node-positive, hormone receptor positive and HER2-neu normal breast cancer	III	3400	Breast

GU=Genitourinary; GI=Gastrointestinal

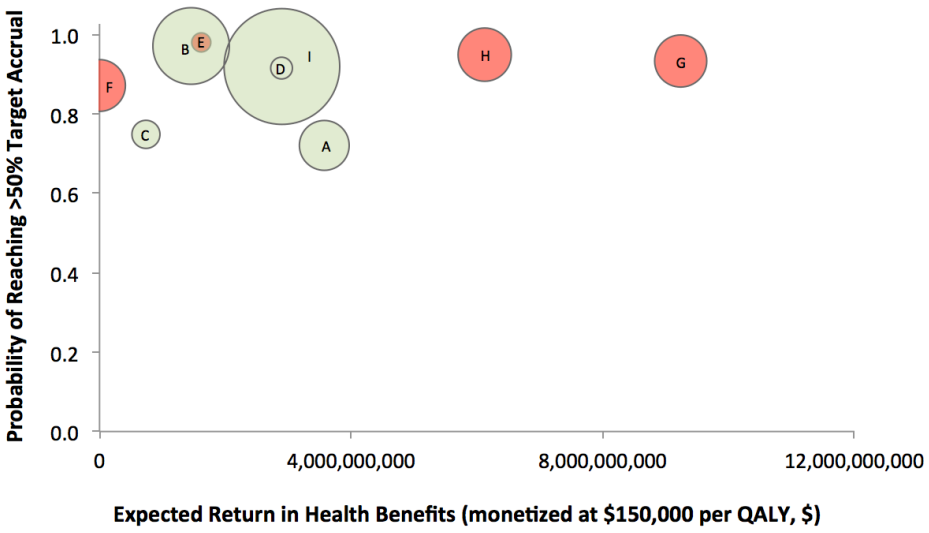
Table 2. Expected return of each trial proposal in health benefits and net benefits and probability of achieving >50% target accrual.

Proposal ID	Probability of achieving >50% target accrual	Expected return in health benefits only	Expected return in net benefits	Risk-adjusted expected return in health benefits only	Risk-adjusted expected return in net benefits
A	0.72	4.95 billion	4.75 billion	3.57 billion	3.42 billion
B	0.97	1.50 billion	-3.70 billion	1.46 billion	-3.61 billion
C	0.75	735 million	-965 million	551 million	-724 billion
D	0.92	3.15 billion	-850 million	2.89 billion	-779 billion
E	0.98	1.65 billion	-150 million	1.62 billion	-147 billion
F	0.85	*	*	*	*
G	0.93	9.90 billion	2.60 billion	9.24 billion	2.43 billion
H	0.95	6.45 billion	2.55 billion	6.12 billion	2.42 billion
I	0.92	3.15 billion	1.45 billion	2.90 billion	1.34 billion

*We could not estimate the expected return for one trial proposal in the sample. We assumed it had a value of $0, which means the overall results are conservative because this proposal was not included in the current portfolio (or either alternative portfolio).

Figure 1. The probability of accrual success by expected clinical return of SWOG's (A) current portfolio and (B) hypothetical alternative portfolio in which trial concepts were selected to optimize risk-adjusted clinical return subject to a constraint on the total number of patients enrolled equal or less than that observed in the current portfolio. Bubble size is proportional to sample size of the proposed trial. Red bubbles were not included in the portfolio; green bubbles were included.

A)



B)

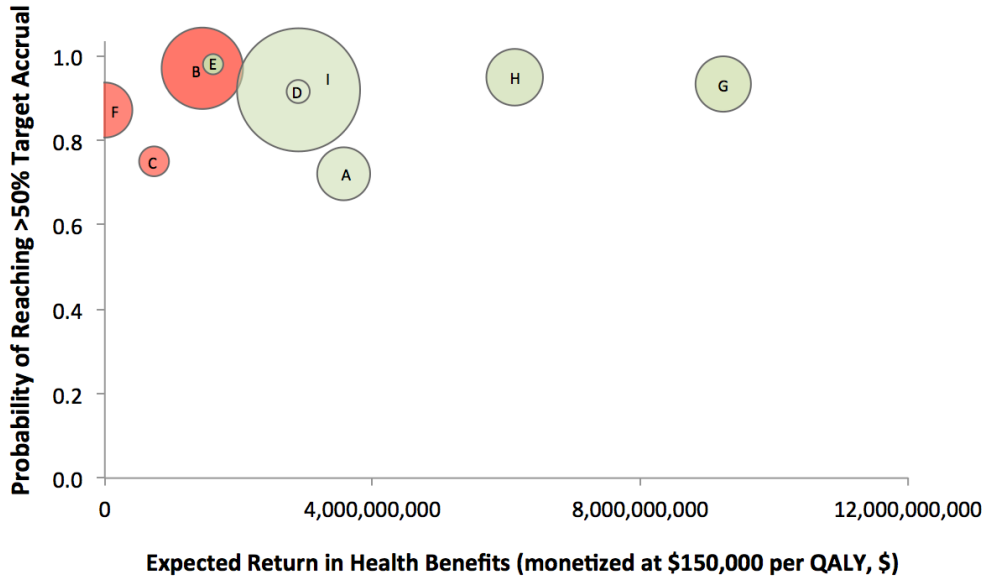
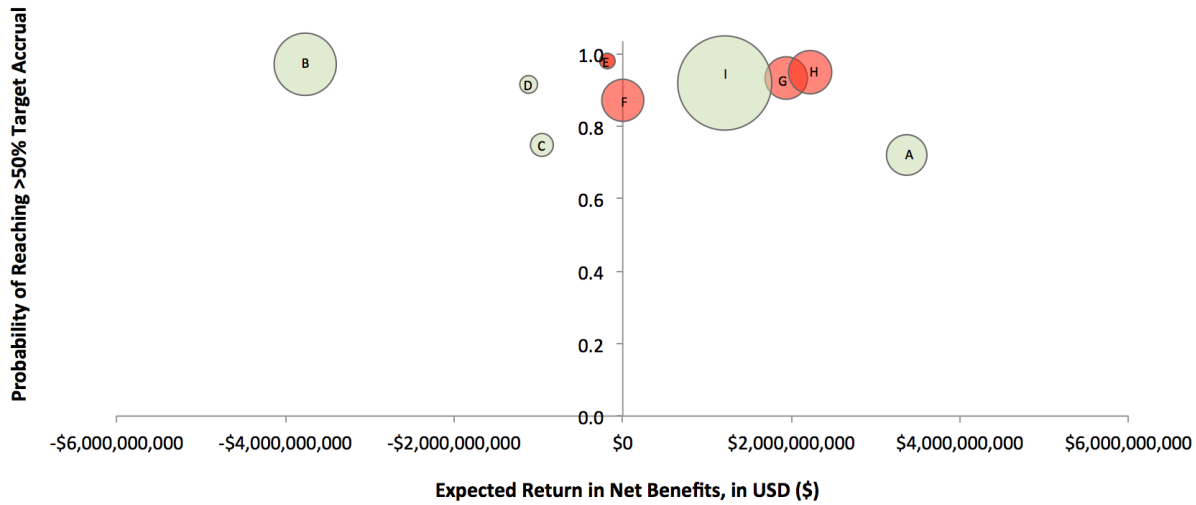
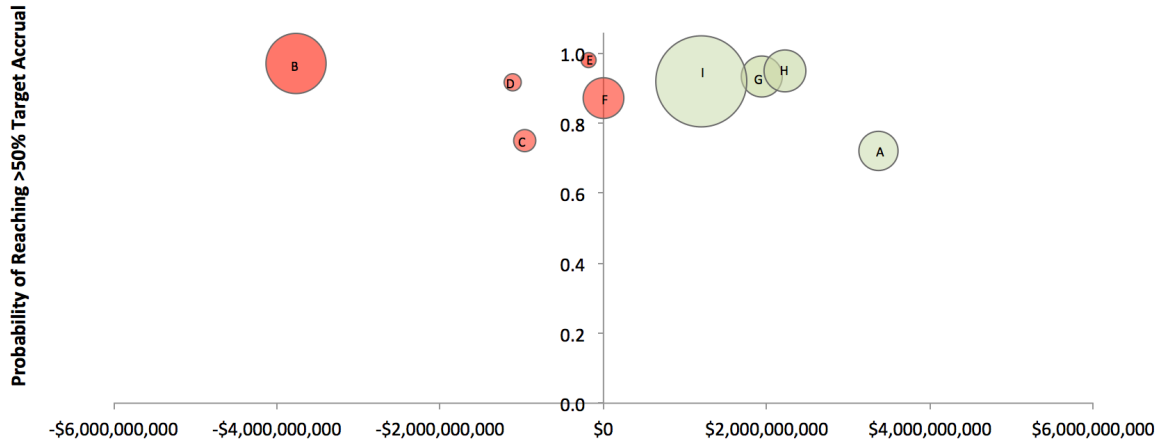


Figure 2. The probability of accrual success by expected economic return of SWOG's (A) current portfolio and (B) hypothetical alternative portfolio in which trial concepts were selected to optimize risk-adjusted economic return subject to a constraint on the total number of patients enrolled equal or less than that observed in the current portfolio. Circle size is proportional to sample size of the proposed trial. Red bubbles were not included in the portfolio; green bubbles were included.

A)



B)



Appendix

Appendix A: Identification and Classification of Clinical Condition(s) Studied in Prediction Model (Chapter I)

Appendix Table I. Total number of clinical trials studying each of the clinical conditions evaluated by one of the NCTN-supported trials included in our main analyses.

Clinical Condition	Text Search Terms	Number Trials Sponsored by NCTN	Number Trials Not Sponsored by NCTN
Anal	anal, anus	4	41
Bladder & Uretheral	bladder, urothe, ureth, urinary	23	167
Bile	bile, biliary	5	60
Brain & Central Nervous System	brain, central nervous system, gliobastoma, glioma, cns	37	436
Breast	breast	104	1184
Cervical	cervic, cervix, fallopian	54	233
Colon & Rectal	colon, colorectal, rectal, rectum	53	591
Endometrial	endometrial, uterine, uterus	68	255
Esophageal	esophageal	24	183
Kidney	kidney, renal	31	315
Larynx	larynx, laryngeal	4	38
Leukemia	leukemia, hemato	66	950
Liver	liver, hepatic, hepato	16	334
Lung & Bronchus	lung, bronch	94	995
Hodgkin's Lymphoma	Hodgkin [but NOT any terms for Non-Hodgkin's lymphoma, see below]	10	102
Non-Hodgkin's Lymphoma	non-hodgkin, nonhodgkin, mantle cell, t-cell lymphoma, t cell lymphoma, b-cell lymphoma, b cell lymphoma, burkitt, lymphocytic lymphoma	55	641
Melanoma	melanoma	23	347
Myeloma	myeloma, plasmacytoma	20	330
Oral	oral, mouth, pharyn, salivary gland	16	250
Ovary	ovar	57	356
Pancreas	pancreas	21	327
Prostate	prostate, prostatic	54	675
Stomach	gastric, stomach	15	191
Testis	testi	3	21
Vulvar	vulva	5	13
Lymphoma, NOS*	lymphoma, hemato	7	190
Sarcoma	sarcoma	45	278
Neuroblastoma	neuroblastoma	3	52
Mesothelioma	mesothelioma	11	44
Head & Neck, NOS	head, neck, h&n	40	318
Thymoma	thymoma, thymic	1	14
Penile	penile	1	4
Merkel	merkel	1	3
Trophoblastic	trophoblast	5	6
Neuroendocrine	neuroendocrine, islet cell, net	2	53
Gastrointestinal Stromal Tumor	gastrointestinal stromal, gist	3	48
Waldenstrom	waldenstrom, macroglobulinemia	3	21
Non-specific cancer condition	[includes cancers of 'unknown primary' and symptom management or supportive care in non-specific cancer conditions]	33	250

*Not including those identified as Hodgkins or Non-Hodgkins Lymphoma.

We verified the text-mining algorithm by manually evaluating its performance in a random sample of 100 trials drawn from the complete dataset (4 were NCTN-sponsored). The initial algorithm correctly classified all trials except 4 of 7 in lymphoma because we did not exclude non-Hodgkin's lymphoma from the Hodgkin's lymphoma classification. We therefore modified our algorithm and verified that it correctly classified conditions in an additional sample of 25 trials that included any 'lymphoma' term.

Clinical categories are not mutually exclusive (i.e. overlap is possible within trials) and are only collectively exhaustive of NCTN-sponsored trials. In other words, certain clinical conditions are not represented (e.g. basal cell carcinomas) if there were no late-phase NCTN-sponsored trials in the condition included in our final dataset.

Appendix B: Literature Review of Trial Level Risk Factors of Poor Accrual

Given the large number of studies that have addressed accrual in cancer trials, we conducted two pragmatic and more targeted searches that were limited to either (a) previously published reviews, or (b) studies within a cooperative group or network setting. The pre-specified search terms were: clinical trial[MeSH Terms] AND cancer[MeSH Terms] AND (particip* OR accru* OR feasib* OR enroll* OR recruit*). We additionally selected the review filter on PubMed for (a) whereas for (b) we included an additional search term (cooperative OR network).

In total we identified (a) 81 and (b) 79 previously published papers that met our initial inclusion criteria. We reviewed the titles and abstracts of these studies to identify a subset of (a) 15 and (b) 23 that appeared relevant to our study question. We excluded studies that evaluated accrual exclusively in pediatric or adolescent settings, but included studies that reported quantitative, qualitative, or expert opinion or commentary on accrual challenges as our goal was to develop as complete a conceptual model as possible and we did not wish to exclude from consideration putative factors that currently lacked empirical evidence. Details regarding the reasons for inclusion or exclusion of these studies in our final analysis and the key findings from each study that was included are summarized in Appendix Table II.

Appendix Table II. Summary of previously published studies in cooperative group or network settings that were included in the first-level review (n=23).

	PMID	Included in final review?	Rationale for exclusion, or study setting if included	Key findings
1	24902923	No	Only evaluated physician-related factors that are not likely to differ across trials (e.g. physician age or specialty); no trial-level variation	
2	24130252	No	Recommendations from ASCO-Trial Accrual Symposium on strategies to improve accrual; did not report specific barriers or challenges	
3	7966396	No	Physician opinion regarding toxicity risk in Phase I studies only	
4	6717508	Yes	Survey of 94 NSABP principal investigators asking why they were not entering eligible patients in a trial to compare segmental mastectomy and postoperative radiation, or segmental mastectomy alone, with total mastectomy	▪ Concern that the doctor-patient relationship would be affected by a randomized clinical trial ▪ Difficulty with informed consent ▪ Dislike of open discussions involving uncertainty
5	21878447	Yes	Challenges to accrual predictions to phase III cancer clinical trials: a survey of study chairs	▪ Therapeutic trials more likely to achieve sufficient accrual than nontherapeutic trials [NS]

			and lead statisticians of 248 NCI-sponsored trials.	▪ Trials studying chemotherapy or immunotherapy more likely to achieve sufficient accrual than those studying radiation therapy or surgical procedure [NS] ▪ Trials with a placebo arm less likely to achieve sufficient accrual [NS]
6	21060029	Yes		▪ Better accrual in trials evaluating a new investigational agent ▪ Poorer accrual in trials with randomized design
7	20808551	No	Survey of sites enrolling patients onto cooperative group trials that address site-specific information only (no trial-level variation)	
8	19900858	Yes	Analyzed accrual to selected phase II and phase III cooperative group non-small-cell lung cancer (NSCLC) trials	▪ Accrual to multimodality trials was poorer than single modality trials ▪ Poorer accrual to trials involving radiation or surgery alone versus chemotherapy ▪ Trend towards better accrual in advanced NSCLC versus early stage disease.
9	19711497; (18612153)	No	Only evaluated patient-related factors that are not likely to differ across trials; no trial-level variation	
10	19805677	No	Did not evaluate challenges to patient accrual	
11	19237631	No	Did not evaluate challenges to patient accrual	
12	18802158	Yes	Survey sent to Ontario-based cancer centers who treated women with breast cancer and cooperative pharmaceutical companies identified by experts in breast cancer field	▪ Poorer accrual in trials with placebo, non-metastatic versus metastatic setting, and shorter enrollment window from incident event (e.g. diagnosis, surgery) to study entry.
13	18650170	Yes	Summary of recommendations from a 1-day symposium that addressed the current challenges of NSCLC clinical trial accrual, hosted by the Coalition of Cancer Cooperative Groups	▪ Compelling research question relevant to current clinical practice ▪ Financial reimbursement that covers the cost of implementing the study and provision of adequate and trained resource support ▪ Simple study design ▪ All treatment arms viewed as acceptable ▪ Short time from letter of intent submission to trial activation
14	17092349	Yes	Analysis of patient eligibility for and reasons for non-entry into phase I trials in a single hospital setting	▪ Patients often ineligible due to poor performance status, too many prior treatments, or rapid disease progression ▪ Primary reasons for non-entry were patient refusal, other treatment recommended first, and lack of available trials
15	16721802	No	Discussion of biopsychosocial human	

			processes that may affect accrual in surgical oncology trials	
16	15860871	Yes		▪ Older age is barrier to clinical trial enrollment
17	15265967	Yes	Evaluation of state mandates for payer coverage of clinical	▪ Overall state coverage policies ensuring reimbursement for routine medical care costs were not associated with a significant increase in trial enrollment of patients with private insurance ▪ Subgroup analysis of phase II trials showed enactment of coverage policies was associated with significant increase in enrollment compared to states without coverage policies.
18	15082724	No	Single institution study	
19	12663731	Yes	Why older patient don't enroll	▪ Protocol exclusion criteria and functional status limitations were associated with lower elderly participation
20	12610181	No	Survey of attitudes of American adults without cancer toward participation in cancer clinical trials; did not evaluate any differential factors of attitudes towards enrollment	
21	10715289	Yes	Study of physicians reluctance for referring breast cancer patients to clinical trials.	▪ Older patients and those with worse prognosis were less likely to be referred for clinical trials ▪ Patients who delayed treatment decisions were more likely to participate [note: biased result] ▪ Oncologists less likely to refer patients if entry criteria were more stringent or onerous
22	6702720	No	Did not evaluate challenges to patient accrual	
23	7070403	No	Did not evaluate challenges to patient accrual	

NS=not significant

Appendix Table III. Summary of previously published systematic reviews included in the first-level review (n=15).

	PMID	Included in final review?	Rationale for exclusion, or study setting if included	Key findings
1	24130252	N/A	Included in table above	
2	23478543	No	Did not evaluate challenges to patient accrual	
3	22425219	No	Did not evaluate challenges to patient accrual	

4	22339743	Yes	Reviews the current literature addressing the obstacles to accrual excluding those related to protocol design	▪ Key physician-related factors associated with accrual difficulty were: concerns about treatment arms, earlier stage disease, time commitment for trial, preference for a particular treatment, perception of importance of clinical question, entry requirements. ▪ Key patient-related factors associated with accrual difficulty were: dislike of randomization, concerns about toxicity, desire to choose another treatment, stringency of eligibility criteria, inconvenience, placebo arm in trial.
5	22135196	No	Findings were highly specific to colorectal cancer screening studies and not generalizable	
6	21059572	Yes	Review of "what is known about the factors that influence cancer clinical trial decision making"	▪ Existence of alternative treatment options, worse benefit to risk profiles, greater time and travel requirements, and worse general health characteristics were associated with lower likelihood of participating in clinical trial.
7	20683424	No	Did not evaluate challenges to patient accrual	
8	18650170	N/A	Included in table above	
9	17884592	Yes	Systematic review. Objective was to investigate the barriers, modifiers, and benefits involved in participating in randomized controlled trials of cancer therapies as perceived by health care providers and patients.	▪ Patient-related factors associated with declining trial enrollment were: treatment preference (either for or against a specific treatment arm) and greater uncertainty (of side-effects or outcomes) ▪ Health system-related factors associated with barriers to trial enrollment were: greater time (extra work, discussions with patients, ethics submissions), greater resources requirements, lack of trial having a good scientific rationale, trial not designed to be in line with standard practice, or protocol not easy to comply with, and lack of trial relevance.
10	16455478	Yes	Meta-analysis and systematic review of patient-reported barriers to participation in clinical trials in cancer	▪ Patient reported barriers to participations included: concerns with the trial setting; dislike of randomization; discomfort with research process; complexity and stringency of the protocol; presence of a placebo or no-treatment group; potential side-effects; being unaware of trial opportunities; idea that clinical trials are not appropriate for serious diseases; fear that trial involvement would have a negative effect on the relationship with their physician; and their physician's attitudes towards the trial.
11	15860871	N/A	Included in table above	
12	12787008	Yes	Review and commentary on reasons for non-	▪ Trial-level factors associated with poor accrual were increased

			participation in clinical trials, with specific reference to the field of cancer research.	burdens of trial participation for the individual (demands on time, travel difficulties, duration of trial), and objection to randomization.
13	11966830	No	Did not evaluate challenges to patient accrual	
14	9349695	No	Discussion of patient participation in cancer chemoprevention trials. Did not report on specific barriers to accrual. [Re-CHECK this one]	
15	1962228	Yes	Review of literature on accrual to cancer therapy trials	▪ Trial-level factors associated with poorer accrual included: more numerous and stricter eligibility criteria, 'no treatment' arms and treatment arms of unequal attractiveness

Appendix C: Key Informant Interviews of Trial Level Factors of Poor Accrual (Chapter I)

Semi-Structured Interview Guide for Assessing Cancer Clinical Trial Feasibility

Introduction

Thank you for agreeing to meet with me. I'm a PhD student in UW's Pharmaceutical Outcomes Research and Policy Program. I'm interested in challenges with completing cancer clinical trials, particularly with respect to patient accrual and in trials sponsored by the cooperative groups. For one Aim of my dissertation, I am collecting and analyzing data about the experiences and opinions regarding clinical trial accrual from individuals who are involved in cancer clinical trials, such as yourself. Our goal is to use the information you and others provide to develop new tools to help improve the process of designing and prioritizing cancer clinical trials.

I will ask you a series of questions, but you are also encouraged to speak freely without being prompted by a question from me. If it is okay with you, I would like to digitally record this interview. If you would like me to stop recording at any time, please let me know and I'll turn off the recorder. Also, please remember that you can always decline to answer any questions and you may decline participation at any time. I think we're scheduled for 30 minutes. Is this still ok for you?

Interview Questions

I. Background and experience of interviewee
   a. To begin, please briefly describe the nature of your work in cancer clinical trials. How many clinical trials have you been involved in, and in what capacity? What are your current and/or past responsibilities with respect to cancer clinical trials in general, and with cooperative group trials in particular?

I. Open-ended questions to elicit experiences regarding trial feasibility and accrual challenges.
   a. Next, I would like to ask you some general questions about challenges with completing clinical trials in cancer.
      i. What do you see as the primary challenge(s) to successfully completing cancer clinical trials, both generally and specifically for cooperative group-sponsored trials?
         1. [*If participants identify more than one challenge, I will also ask them to rank these factors by importance.*]
         2. [*If accrual is not mentioned in response to the above question*]: In your experience, have you found that accrual to clinical trials is an important challenge to successfully completing cancer clinical trials, both generally and specifically for cooperative group-sponsored trials? If so, why?
      ii. In your experience, have you found that it is more difficult to recruit patients to some cancer clinical trials compared to others? If so, what do you think are the primary causes for this difference, in general and/or for specific trials? Could you explain with an example, either real or hypothetical?

II. Probing questions to explore informants' perceptions and opinions regarding specific hypothesized factors identified from literature review; focusing on factors that are not yet well studied.

a. Now I would like to ask you some questions regarding specific factors that may or may not be associated with accrual to cancer clinical trials.

i. Based on your experience, to what extent do you think the following factors affect, or could affect, accrual to a cancer clinical trial? [*I will present the following list one at a time, and if participants indicate that any are important, I will ask them to elaborate and provide detailed examples (real or hypothetical) of how these factors could impact accrual. I will eliminate from the list any factors identified from participants in the section above*].

1. Existence of other clinical trials for the same patient population
2. Whether or the drug is already FDA approved
3. Cost of the intervention(s) being studied
4. Number of eligibility criteria in the trial
5. Time commitment of patients to be involved in the trial, including time for treatment and/or follow up
6. How similar the intervention(s) being studied is to standard care
7. Whether the trial has industry sponsorship or not
8. Whether the trial uses a placebo control or an active comparator

III. Addressing challenges

a. Thank you for your comments about the key challenges for completing cancer clinical trials. Regarding the factors you mentioned that were important [*review list with interviewee*], do you have any thoughts or suggestions about approaches to address these challenges?

IV. Wrap up and final thoughts

a. Thank you for your time and valuable feedback today; I really appreciate all of your comments. Do you have any additional thoughts or comments that you would like to share?

Appendix D: Accounting for Misclassified Number of Competing Trials Launched Prior to 2007 (Chapter I)

Overview

The number of trials launched prior to September 2007 is measured with error because registration was not uniformly required; however, trials launched after September 2007 provide a sample in which there is no longer measurement error. We therefore used the sample of trials started after September 2007 as a validated subset in which the level of competition had been measured without error. We recalibrated the measure of competition in trials started before September 2007 using missing data techniques (i.e. multiple imputation), following the same approaches described in detail elsewhere.

Comparing Competition as Measured Before and After September 2007

We evaluated the total number of late phase cancer clinical trials registered on ClinicalTrials.gov in each year after 2007. We found relatively consistent total number of trials over time: 1469, 1443, 1348, and 1429 launched in 2008, 2009, 2010 and 2011, respectively. We therefore assumed that there were approximately as many late phase cancer trials launched in each year prior to 2008 as well. The total number of trials launched each year that was registered on ClinicalTrials.gov increased over time (Appendix Table IV).

We next assumed that trials not registered on ClinicalTrials.gov were missing at random for the purposes of these analyses conditional on the amount of time prior to September 27, 2007. We empirically evaluated this assumption in several ways. First, we explored whether there were any differences in the proportion of trials that were launched in each of the 39 distinct clinical conditions shown in Appendix Table xx prior to 2007 or after 2008. We identified 3 conditions with significant differences (at the $p<0.1$ level) – Hodgkin's lymphoma, leukemia, and esophageal cancers – however, in each of these settings the proportion of trials was lower after 2008 than prior to 2007, suggesting that these trends were more likely general decline in clinical research in these settings than biased registration on ClinicalTrials.gov. Second, we explored whether the distribution of incidence of conditions being studied differed in trials launched before or after September 2007. Such a difference might occur if trials were more or less likely to register trials in rare conditions, for example, which could potentially bias our findings as our measure of competition is incidence-adjusted. However, we found a nearly identical distribution of incidence of conditions being studied before or after 2007 (Appendix Figure I).

We therefore treated the portfolio of trials registered before September 2007 as representative of the proportion of trials started in each clinical condition over time. We recalibrated the total number of trials in each condition by multiplying the proportion of trials in each clinical condition by the ratio of observed to expected total trials (i.e. a Bayes factor), calculated quarterly. To incorporate uncertainty in this recalibration, we took 50 bootstrap samples with replacement of the entire dataset, calculate a Bayes adjusted level of competition, and combined the estimation results using Rubin's rules (MI commands in STATA).

Sensitivity Analyses for Measure of Competition

We conducted several sensitivity analyses to assess the robustness of our results with respect to the recalibrated measure of competition. First, we explored the association between competition and poor accrual in a pre-specified subgroup of trials that started after September 27th, 2008 (one year after the requirement to register all new trials). There were 130 NCTN-sponsored trials in this analysis, 31 of which experienced poor accrual. Overall there was a strong association between level of competition and poor accrual (OR per: 1.88 [95% CI: 1.18, 2.99]).

Second, we constructed a prediction model using only trials launched in 2000 and 2004 and evaluated whether including a measure of competition improved discrimination of predictions made for trials started after 2008. Including competition in the model improved the AUC in the out of sample predictions from 0.692 to 0.714.

Third, we evaluated how our main results would have changed without including a measure of competition. If we omitted competition from the set of possible predictors, the remaining variables included in our final prediction model would not have changed. The bootstrap corrected AUC of the model without competition was 0.71.

Lastly, we explored different ways to measure competition, specifically calculating the total number of trials opened within the previous two or three years of the index trial, or counting all trials that were open for enrollment at the time the index trial started. Overall our results were very similar across definitions, with the effects slightly attenuated when longer time frames were used. For example, the odds ratios were 1.30 (95% CI: 1.16, 1.47) and 1.03 (95% CI: 1.01, 1.04) for 2-year and 'all open' measures of competing trials.

As the goal of these analyses is prediction, we included the measure of competition that appeared the have the greatest predictive properties, which we evaluated in several ways. When all measures were included in the stepwise regression models, the measure of competition based on trials opened in the previous one year was consistently included in the final model, whereas none of the other measures of competition were included. Forcing the inclusion of additional measures of competition into the final model actually lowered the AUC slightly (by less than 0.0005 points for all). We also conducted an exploratory analysis using least angle regression (LARs) methods to select predictors using the *lars* package in STATA. Selecting predictors using LARS resulted in a much larger final model (a total of 23 variables included); however, only the 1-year measure of competition was included. Given the consistency of these results we felt confident that the measure of competition measured by the number of trials opened in the previous year provided the best predictive properties among the set considered.

Appendix E: Additional details about generating prior distributions of treatment effect (Chapter II)

Example generating prior distribution using expert elicitation: The main idea is to use the null and alternative hypotheses as anchors and ask experts the chance the alternative hypothesis is true and the chance the new treatment is worse than the comparator. Here's an example:

- From the capsule sample size calculations, we obtain the exponential hazard rate of the comparator treatment as 0.045, and under the alternative the rate using the new treatment as 0.034 (i.e., HR=0.75).
- Hypothetical expert opinion (note: this would be a very optimistic prior):
    - 50% chance the alternative is true —> median of prior = 0.034
    - 15% chance the new treatment is worse than comparator—> 85th percentile of prior = 0.045
- Fit a gamma distribution to these judgments
    - Parameters: shape = 12.7, rate = 364
    - Expected value of hazard rate for new treatment is 0.35; it's also easy to spit out a pdf/cdf to verify whole distribution with experts, as needed

*For the retrospective review of capsules we are using the following evidence-based assumptions:

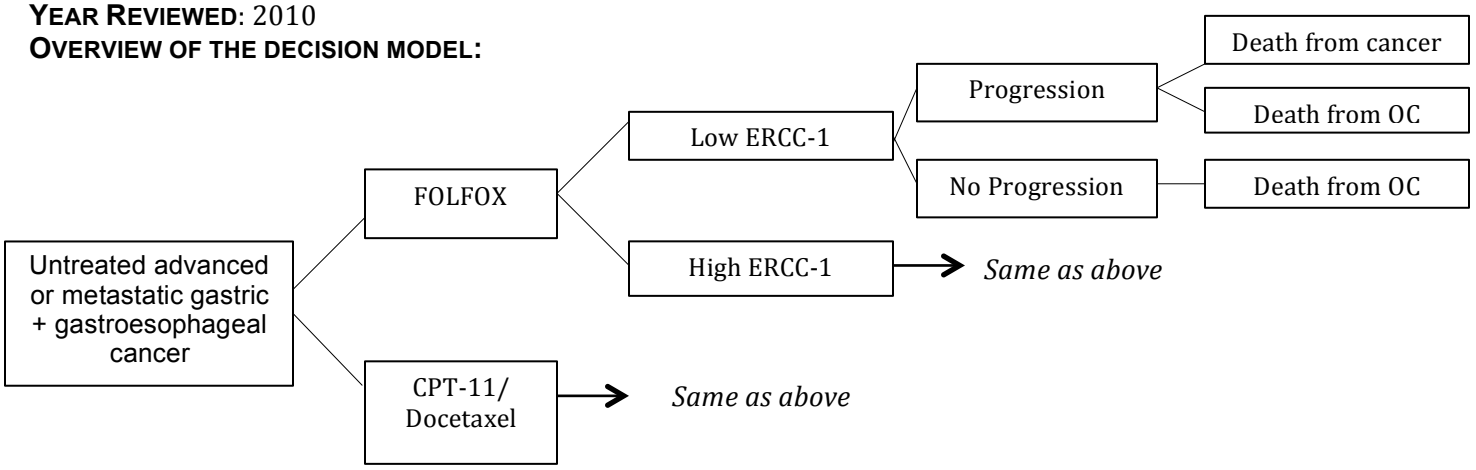
- 25% chance the alternative is true (e.g. 25th percentile = 0.034)
- 40% chance the new treatment is worse or 60% chance it works as well as or better than comparator (e.g. 60th percentile of prior = 0.045)

Appendix F: Additional details about each minimal model included in the VOI analyses (Chapter II)

A Randomized Phase II Pilot Study Prospectively Assigning Treatment for Patients Based on ERCC1 for Advanced/Metastatic Gastric Cancer or Gastroesophageal (GE) Junction Cancer

Year Reviewed: 2010

Overview of the Decision Model:



OC = Other Causes

Summary of Modeling Inputs:

Parameter	Value	Source
Trial Inputs		
Length of accrual + follow up	5.5 years	Capsule
Sample size	200	Capsule
Decision Model Inputs		
Median PFS for high ERCC-1 FOLFOX/low ERCC-1 CD	4 months	Capsule
Hypothesized Median PFS for high ERCC-1 CD/low ERCC-1 FOLFOX	6.2 months	Capsule
Average time between progression and death	4 months	(1-3)
Probability high ERCC-1 CD/low ERCC-1 FOLFOX is superior	60%	Assumption
Probability high ERCC-1 CD/low ERCC-1 FOLFOX significantly superior	25%	Assumption
Utility, advanced gastric cancer	0.75	Assumption
Average age of patient population at enrollment	57	Assumption
Annual treatment costs of advanced gastric cancer	$114,000	(4)
Population Projection Inputs		
Number affected individuals per year	14,500	SEER
Time horizon for information	10 years	Assumption

Value of Information (VOI) Results:

	Per Patient who Faces Decision	Entire Patient Population
Clinical VOI	$9200	$490 million
VOI	-$23,000	-$1.2 billion

The VOI is lower than the clinical VOI because the potential clinical benefit comes at a substantial increase in treatment costs; in this case, the VOI is negative because the increase in treatment costs would outweigh the expected clinical benefits at a willingness to pay threshold of $100,000 per QALY. Please see the next page for details.

EXPLANATION OF MODELING INPUTS:

Decision model: The decision model schematic represents the key health states through which patients move in the model. For this decision model, patients with advanced or metastatic gastric cancer receive either FOLFOX or CPT-11/Docetaxel after which they can progress and ultimately die from gastric cancer or other causes. We assume that outcomes under current standard of care are represented by the null hypothesis (i.e., a median PFS of 4 months).

Health state transitions: The median progression-free survival (PFS) for high ERCC-1 FOLFOX/low ERCC-1 CD was 4 months based on data presented in the capsule. Under the alternative hypothesis, the median PFS for trametinib was 6.2 months (HR_{PFS} =1.55). We assumed that metastatic gastric cancer patients would die from the disease on average 4 months after a progression(1-3).

Utilities: We assumed a utility of 0.75 (95% CI: 0.55, 0.95), which is similar to the utility for gastrointestinal stromal tumors (0.77) and metastatic pancreatic cancer (0.73)(5, 6). We did not identify any studies reporting the health state utility values of patients with advanced gastric cancer.

Treatment costs: We assumed that the annual costs for gastric were approximately $114,000(4). As a simplifying assumption we did not include the differential cost of protocol related treatment because the primary hypothesis of this trial is that FOLFOX will be superior in the low ERCC-1 group and CPT-11/docetaxel will be superior in the high ERCC-1 group; with approximately 50% of patients expected in each group (based on capsule data) there is not expected to be a difference in overall costs.

Population projection: Approximately 14,500 individuals are diagnosed with advanced gastric cancer each year.

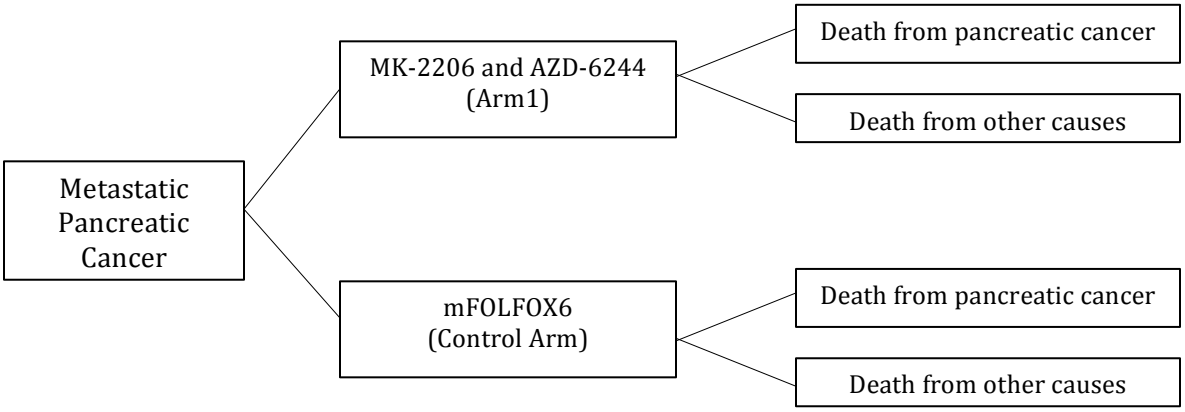
SUMMARY OF VOI RESULTS:

The expected health benefits of acquiring additional evidence for the decision between FOLFOX or CPT-11/Docetaxel with this trial proposal is approximately 0.09 quality-adjusted life years (QALYs) per individual who faces the decision. If we monetize health benefits at $100,000 per QALY, this is equivalent to $9200, which is the per-patient clinical VOI. If we include the costs of treatment, the net present value of acquiring additional evidence is -$23,000 per individual who faces the decision. The VOI is lower than the clinical VOI because the potential clinical benefit would come at a substantial increase in treatment costs; in this case, the net present VOI is negative because the increase in treatment costs outweighs the expected clinical benefits at a willingness to pay threshold of $100,000 per QALY. Taking into account the number of individuals who will face this decision in the near to immediate future (10 years), the expected clinical VOI is approximately $490 million and the expected societal net benefit is -$1.2 billion. The VOI is not positive unless we are willing to pay more than $350,000 per QALY.

RANDOMIZED PHASE II CLINICAL TRIAL OF AZD-6244 AND MK-2206 VS MFOLFOX IN PATIENTS WITH METASTATIC PANCREATIC CANCER AFTER PRIOR CHEMOTHERAPY

YEAR REVIEWED: 2011

OVERVIEW OF THE DECISION MODEL:



SUMMARY OF MODELING INPUTS:

PARAMETER	VALUE	SOURCE
TRIAL INPUTS		
Length of accrual + follow up	3.5 years	Capsule
Sample size	120	Capsule
DECISION MODEL INPUTS		
Median OS with mFOLFOX6	6 months	Capsule
Hypothesized Median OS with MK-2206 and AZD-6244	9 months	Capsule
Probability MK-2206 and AZD-6244 is superior	60%	Assumption
Probability MK-2206 and AZD-6244 is significantly superior	25%	Assumption
Utility, metastatic pancreatic cancer	0.73	(6)
Average age of patient population at enrollment	60	Assumption
POPULATION PROJECTION INPUTS		
Number affected individuals per year	24,600	SEER
Time horizon for information	10 years	Assumption

VALUE OF INFORMATION (VOI) RESULTS:

	PER PATIENT WHO FACES DECISION	ENTIRE PATIENT POPULATION
CLINICAL VOI	$16,000	$2.1 billion
VOI	--	--

EXPLANATION OF MODELING INPUTS:

Decision model: The decision model schematic represents the key health states through which patients move in the model. For this decision model, patients with metastatic pancreatic cancer receive either mFOLFOX or AZD-6244 and MK-2206 after which they can die from pancreatic cancer or other causes.

Health state transitions: The median OS for mFOLFOX is 6 months based on data from the capsule. Under the alternative hypothesis, the median OS for trametinib was 9 months.

Utilities: We assumed a utility of 0.73 (95% CI: 0.32, 0.98), based on a study used the EQ-5D instrument to evaluate 186 patients with advanced pancreatic cancer participating in the CALGB 80303 trial. We did not identify any studies reporting the health state utility values of patients with advanced gastric cancer.(6)

Treatment costs: As AZD-6244 and MK-2206 are investigational drugs, they do not yet have a market price and we therefore did not report the VOI estimates including costs.

Population projection: Approximately 24,600 patients are diagnosed with metastatic pancreatic cancer each year. We assumed all of these patients would eventually face a treatment decision between mFOLFOX6 and MK-2206 and AZD-6244.

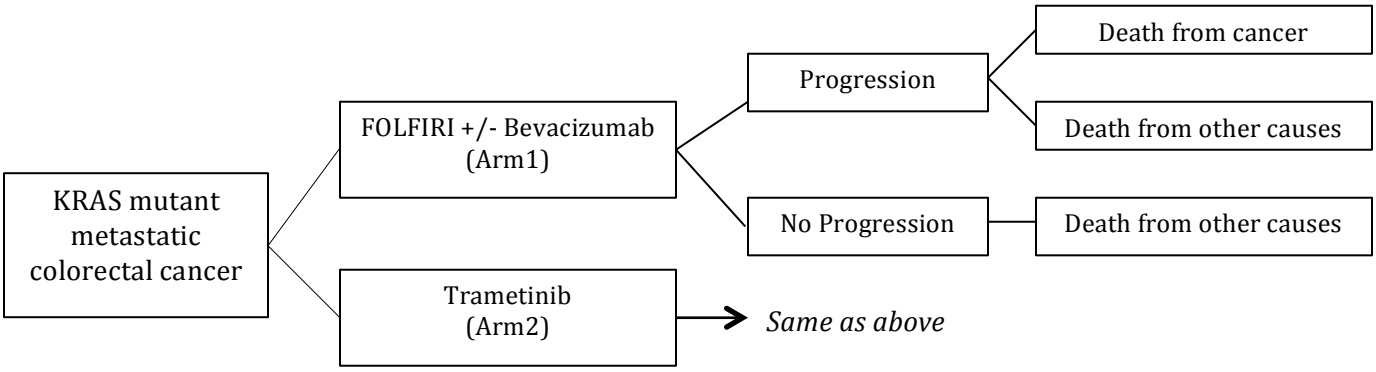
SUMMARY OF VOI RESULTS:

The expected health benefits of acquiring additional evidence for the decision between AZD-6244 and MK-2206 vs mFOLFOX is approximately 0.16 quality-adjusted life years (QALYs) per individual who faces the decision. If we monetize health benefits at $100,000 per QALY, this is equivalent to $16,000, which is the per-patient clinical VOI. Taking into account the number of individuals who will face this decision in the near to immediate future (10 years), the population level clinical VOI is approximately $2.1 billion.

RANDOMIZED PHASE II STUDY COMPARING THE NOVEL MEK INHIBITOR, TRAMETINIB, TO STANDARD OF CARE CHEMOTHERAPY IN PATIENTS WITH KRAS MUTANT METASTATIC COLORECTAL CANCER

YEAR REVIEWED: 2013

OVERVIEW OF THE DECISION MODEL:



SUMMARY OF MODELING INPUTS:

PARAMETER	VALUE	SOURCE
TRIAL INPUTS		
Length of accrual + follow up	2 years	Capsule
Sample size	92	Capsule
DECISION MODEL INPUTS		
Median PFS with FOLFIRI +/- Bevacizumab	3 months	Capsule
Hypothesized median PFS with Trametinib	4.8 months	Capsule
Probability Trametinib is superior to FOLFIRI +/- Bevacizumab	60%	Assumption
Probability Trametinib is significantly superior to FOLFIRI +/- Bevacizumab	25%	Assumption
Utility, metastatic colorectal cancer	0.71	(7)
Average time between progression and death	1.1 years	(8)
Average age of patient population	60	Assumption
Monthly treatment costs of metastatic colorectal cancer	$10,00	(9) (10)
POPULATION PROJECTION INPUTS		
Number affected individuals per year	16,400	SEER, (11)
Time horizon for information	10 years	Assumption

VALUE OF INFORMATION (VOI) RESULTS:

	PER PATIENT WHO FACES DECISION	ENTIRE PATIENT POPULATION
CLINICAL VOI	$9400	$1.1 billion
VOI	-$6400	-$720 million

The VOI is lower than the clinical VOI because the potential clinical benefit comes at a substantial increase in treatment costs; in this case, the VOI is negative because the increase in treatment costs would outweigh the expected clinical benefits at a willingness to pay threshold of $100,000 per QALY. Please see the next page for details.

EXPLANATION OF MODELING INPUTS:

Decision model: The decision model schematic represents the key health states through which patients move in the model. For this decision model, patients with metastatic colorectal cancer can receive either FOLFIRI +/- bevacizumab or trametinib after which they can progress and ultimately die from colorectal cancer or other causes.

Health state transitions: The median progression-free survival (PFS) for FOLFIRI +/- bevacizumab was 3 months based on data presented in the capsule. Under the alternative hypothesis, the median PFS for trametinib was 4.8 months. We derived the average time between a progression and death from colorectal cancer, 1.1 years (95% CI: 0.78, 1.26), from a recent systematic literature review of 50 trials in metastatic colorectal cancer(8).

Utilities: The mean health state utility value for stable metastatic colorectal cancer 0.71 (95% CI: 0.66, 0.76). These values were derived from a recent systematic review and meta-analysis of utility values in colorectal cancer. To simplify the decision model we assumed no change in utility values over time.

Treatment costs: We assumed that the monthly costs for mCRC were approximately $10,000(9). The protocol-related costs for were also approximately $10,000 per month(10, 12). The costs for trametinib are included with the caveat that the treatment was first FDA approved (for melanoma) 2 months after the initial review of this capsule.

Population projection: Approximately 82,100 patients are diagnosed with metastatic colorectal cancer each year (27,400 patients as *de novo* metastatic disease and 54,700 diagnosed as an earlier stage that has progressed)(13). We assumed 40% of patients would have a KRAS mutation (based on data presented in the capsule) and 50% would receive 2nd line therapy following oxaliplatin-based therapy(11) for a total of 16,400 patients each year who would face the treatment decision evaluated by this trial.

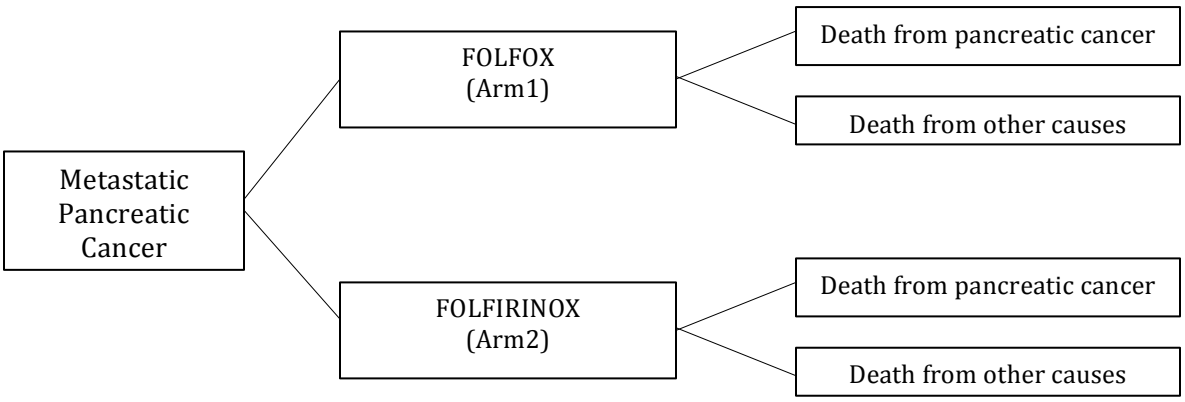
SUMMARY OF VOI RESULTS:

The expected health benefits of acquiring additional evidence for the decision between FOLFIRI +/- bevacizumab or trametinib with this trial proposal is approximately 0.094 quality-adjusted life years (QALYs) per individual who faces the decision. If we monetize health benefits at $100,000 per QALY, this is equivalent to $9400, which is the per-patient clinical VOI. If we include the costs of treatment, the value of acquiring additional evidence is -$6400 per individual who faces the decision. The VOI is lower than the clinical VOI because the potential clinical benefit would come at a substantial increase in treatment costs; in this case, the VOI is negative because the increase in treatment costs outweighs the expected clinical benefits at a willingness to pay threshold of $100,000 per QALY. Taking into account the number of individuals who will face this decision in the near to immediate future (10 years), the expected clinical VOI is approximately $1.1 billion and the expected societal net benefit is -$720 million. The VOI is not positive unless we are willing to pay more than $168,000 per QALY.

A PHASE II RANDOMIZED STUDY OF FOLFIRINOX VERSUS FOLFOX IN PATIENTS WITH METASTATIC PANCREATIC ADENOCARCINOMA

YEAR REVIEWED: 2011

OVERVIEW OF THE DECISION MODEL:



SUMMARY OF MODELING INPUTS:

PARAMETER	VALUE	SOURCE
TRIAL INPUTS		
Length of accrual + follow up	3 years	Capsule
Sample size	190	Capsule
DECISION MODEL INPUTS		
Median OS with FOLFOX6	**Not available**	-
Hypothesized Median OS with FOLFIRINOX	**Not available**	-
Probability FOLFOX6 is superior	**Not available**	-
Probability FOLFIRINOX is significantly superior	**Not available**	-
Utility, metastatic pancreatic cancer	0.73	(6)
Average age of patient population at enrollment	60	Assumption
POPULATION PROJECTION INPUTS		
Number affected individuals per year	24,600	SEER
Time horizon for information	10 years	Assumption

FEASIBILITY ASSESSMENT OF VOI CALCULATIONS:

Although this trial involves a randomization between FOLFOX and FOLFIRINOX, the statistical analysis plan is written as if these two treatments are each non-randomized phase II trials. In other words, the trial is powered to detect a difference between 6 and 10 months, even though the 6 months OS estimate is for a treatment regimen that is not being evaluated as part of this trial (gemcitabine). It is not clear from data presented in the capsule whether the investigators expect both treatments to achieve greater than 6 months OS, and if not, which treatment is hypothesized to be superior. Therefore it is not possible to calculate the VOI for this trial given the data included in the trial capsule. With clarification from the trial investigators regarding the null and alternative hypotheses it may be possible to calculate the VOI.

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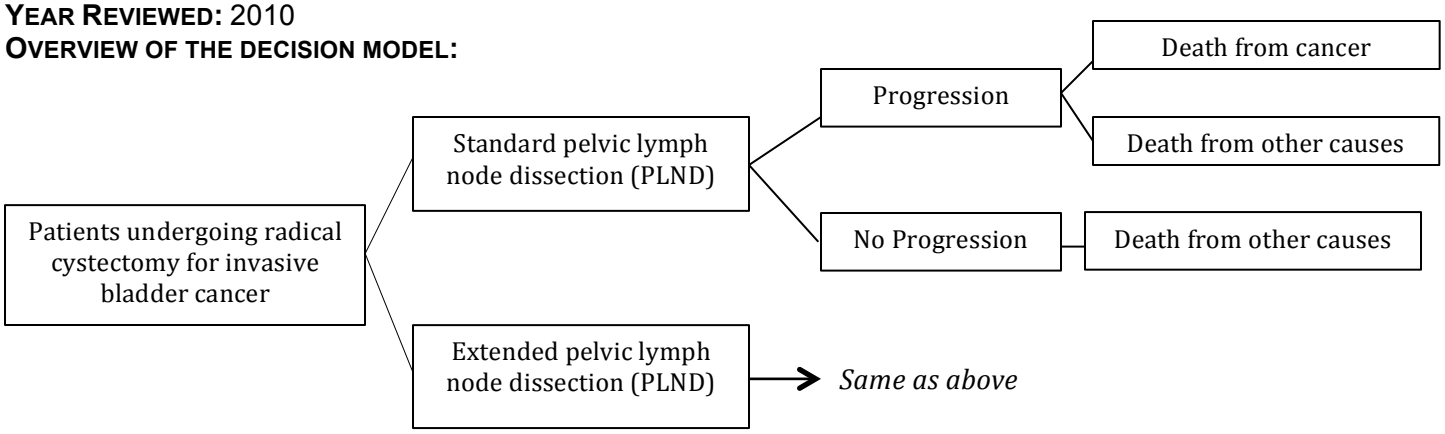
PROSPECTIVE EVALUATION OF THE BENEFIT OF A STANDARD VERSUS AN EXTENDED PELVIC LYMPHADENECTOMY PERFORMED AT TIME OF RADICAL CYSTECTOMY FOR BLADDER CANCER WITH ADJUVANT CHEMOTHERAPY ADMINISTRATION FOR NODE POSITIVE DISEASE

YEAR REVIEWED: 2010

OVERVIEW OF THE DECISION MODEL:



SUMMARY OF MODELING INPUTS:

PARAMETER	VALUE	SOURCE
TRIAL INPUTS		
Length of accrual + follow up	7 years	Capsule
Sample size	630	Capsule
DECISION MODEL INPUTS		
3-year PFS with standard PLND	45%	Capsule
Hypothesized 3-year PFS with extended PLND	55%	Capsule
Probability extended PLND is superior to standard PLND	60%	Assumption
Probability extended PLND is significantly superior to standard PLND	25%	Assumption
Utility, post-cystectomy	0.96	Assumption, (1)
Average time between progression and death	2.5 years	Capsule, Assumption
Average age of patient population	57	Assumption
Annual treatment costs of bladder cancer	$4,000	(2)
POPULATION PROJECTION INPUTS		
Number affected individuals per year	31,400	SEER
Time horizon for information	10 years	Assumption

VALUE OF INFORMATION (VOI) RESULTS:

	PER PATIENT WHO FACES DECISION	ENTIRE PATIENT POPULATION
CLINICAL VOI	$43,800	$3.3 billion
VOI	$42,000	$3.1 billion

EXPLANATION OF MODELING INPUTS:

Decision model: The decision model schematic represents the key health states through which patients move in the model. For this decision model, patients with invasive bladder cancer can receive a radical cystectomy with either a standard or extended pelvic lymph node dissection (PLND) after which they can progress and ultimately die from bladder cancer or other causes.

Health state transitions: The 3-year progression-free survival (PFS) for patients with a standard PLND was 45%, according to data presented in the capsule. We derived the predicted relationship between PFS and OS from data presented in the capsule. Specifically, the capsule reports the 5-year OS survival rate as 45%. Assuming exponential survival (as was done in the capsule) for both PFS and OS, this translates into an average of approximately 2.5 years between progression and death. We assumed the 95% CIs around this estimate were 2 to 3 years. Lastly, we made the simplifying assumption that an extended PLND was not associated with differences in length of stay or blood loss as these outcomes are not likely to have a major impact on overall quality-adjusted life, especially relative to the expected improvements in PFS.

Utilities: We assumed that the utility for patients post-cystectomy would be 0.96 (SE 0.192), following the assumptions used in a previously published cost-effectiveness analysis of radical cystectomy versus intravesical BCG therapy(1). There was a general lack of data available on health state utilities in bladder cancer.

Treatment costs: We assumed that the annual ongoing medical costs for patients with invasive bladder cancer were approximately $4,000(2). We assumed that an extended PLND would not increase the cost of radical cystectomy compared to a standard PLND.

Population projection: Approximately 31,400 individuals are diagnosed with invasive bladder cancer each year. We assumed that all of these individuals would be eligible for radical cystectomy.

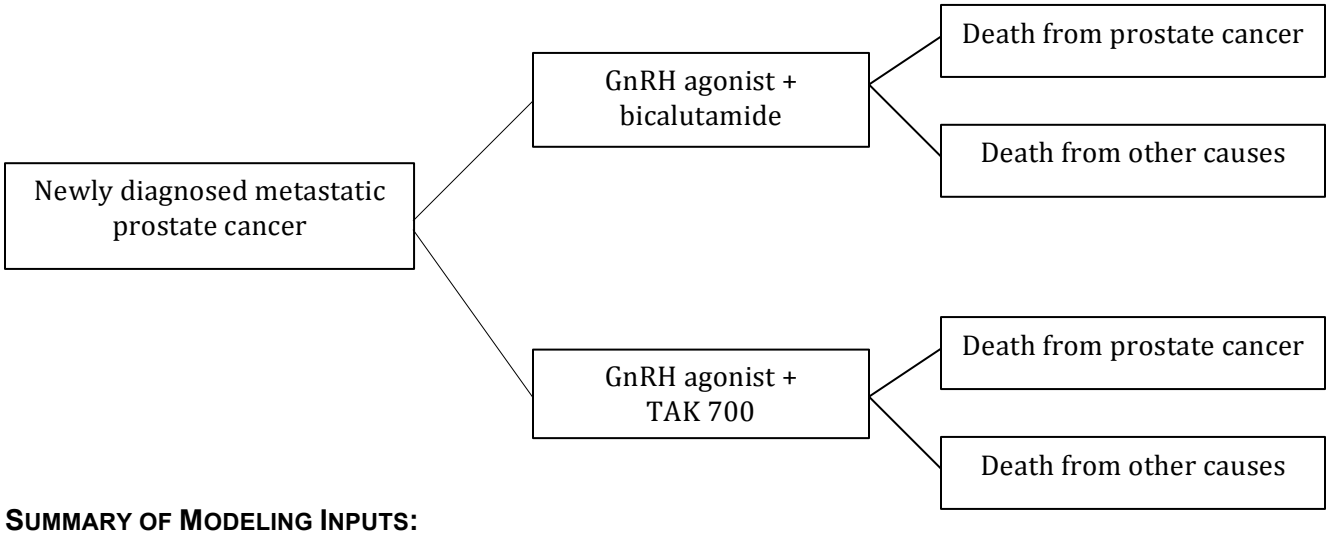
SUMMARY OF VOI RESULTS:

The expected health benefits of acquiring additional evidence for the decision between standard and extended PLND with this trial proposal is approximately 0.44 quality-adjusted life years (QALYs) per individual who faces the decision. If we monetize health benefits at $100,000 per QALY, this is equivalent to $43,800, which is the per-patient clinical VOI. If we include the costs of treatment, the value of acquiring additional evidence is $42,000 per individual who faces the decision. The VOI is slightly lower than the clinical VOI because the potential clinical benefit would come at a small increase in downstream treatment costs. Taking into account the number of individuals who will face this decision in the near to immediate future (10 years), the expected clinical VOI is approximately $3.3 billion and the expected societal value is $3.1 billion.

A PHASE III RANDOMIZED TRIAL COMPARING LHRHA + TAK-700 WITH LHRHA + BICALUTAMIDE IN PATIENTS WITH NEWLY DIAGNOSED D2 PROSTATE CANCER.

YEAR REVIEWED: 2011

OVERVIEW OF THE DECISION MODEL:



SUMMARY OF MODELING INPUTS:

PARAMETER	VALUE	SOURCE
TRIAL INPUTS		
Length of accrual + follow up	8.5 years	Capsule
Sample size	1486	Capsule
DECISION MODEL INPUTS		
Median OS with bicalutamide	54 months	Capsule
Hypothesized median OS with TAK-700	68 months	Capsule
Probability TAK-700 is superior to bicalutamide	60%	Assumption
Probability TAK-700 is significantly superior to bicalutamide	25%	Assumption
Utility, metastatic prostate cancer	0.5	(3)
Average age of patient population	70	Assumption
POPULATION PROJECTION INPUTS		
Number affected individuals per year	35,000	SEER
Time horizon for information	10 years	Assumption

VALUE OF INFORMATION (VOI) RESULTS:

	PER PATIENT WHO FACES DECISION	ENTIRE PATIENT POPULATION
CLINICAL VOI	$14,700	$1 billion
VOI	--	--

EXPLANATION OF MODELING INPUTS:

Decision model: The decision model schematic represents the key health states through which patients move in the model. For this decision model, patients with newly diagnosed prostate cancer can receive a GnRH agonist + bicalutamide or a GnRH agonist + TAK 700 after which they can die from prostate cancer or other causes.

Utilities: We conservatively assumed the health state utility for men with metastatic prostate cancer was 0.5(3). This value was used in a recent NICE assessment of abiraterone for castration-resistant metastatic prostate cancer(3). Other studies have reported similar (0.42)(4) and lower (0.25)(5) utility estimates.

Treatment costs: As TAK-700 is an investigational drug, it does not yet have a market price and we therefore did not report the VOI estimates including costs.

Population projection: Approximately 35,000 individuals are newly diagnosed with metastatic prostate cancer each year according to SEER data.

SUMMARY OF VOI RESULTS:

The expected health benefits of acquiring additional evidence for the decision between a GnRH agonist and either bicalutamide or TAK-700 is approximately 0.15 quality-adjusted life years (QALYs) per individual who faces the decision. If we monetize health benefits at $100,000 per QALY, this is equivalent to $14,700, which is the per-patient clinical VOI. Taking into account the number of individuals who will face this decision in the near to immediate future (10 years), the population level clinical VOI is approximately $1 billion.

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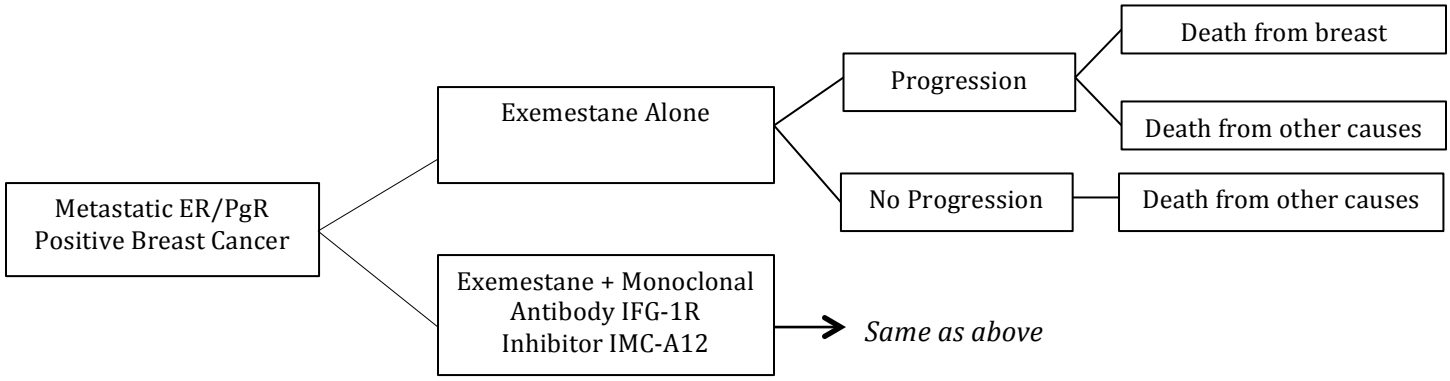
A RANDOMIZED PHASE III TRIAL OF THE STEROIDAL AROMATASE INHIBITOR, EXEMESTANE, VS. A COMBINATION OF EXEMESTANE AND THE MONOCLONAL ANTIBODY IGF-1R INHIBITOR IMC-A12 IN PATIENTS WITH METASTATIC ER/PGR POSITIVE BREAST CANCER

OVERVIEW OF THE DECISION MODEL:



SUMMARY OF MODELING INPUTS:

PARAMETER	VALUE	SOURCE
TRIAL INPUTS		
Length of accrual + follow up	5.4 years	Capsule
Sample size	690	Capsule
DECISION MODEL INPUTS		
Median PFS for Exemestane alone	10 months	Capsule
Hypothesized Median PFS for Exemestane + IMC-A12	13 months	Capsule
Average time between progression and death	12 months	(1, 2)
Probability Exemestane + IMC-A12 is superior	60%	Assumption
Probability Exemestane + IMC-A12 significantly superior	25%	Assumption
Utility, stable metastatic breast cancer	0.76	(3)
Utility, metastatic breast cancer that has progressed	0.59	(3)
Average age of patient population at enrollment	65	Assumption
POPULATION PROJECTION INPUTS		
Number affected individuals per year	37,500	SEER, (4-6)
Time horizon for information	10 years	Assumption

VALUE OF INFORMATION (VOI) RESULTS:

	PER PATIENT WHO FACES DECISION	ENTIRE PATIENT POPULATION
CLINICAL VOI	$48,100	$6.6 billion
VOI	--	--

EXPLANATION OF DECISION MODEL AND KEY INPUTS:

Decision model: The decision model schematic represents the key health states through which patients move in the model. For this decision model, women with metastatic ER/PgR positive breast cancer can receive either exemestane or exemestane + IMC-A12 after which they can progress and ultimately die from breast cancer or other causes.

Health state transitions: The median progression-free survival (PFS) for exemestane was 10 months based on data presented in the capsule. Under the alternative hypothesis, the median PFS for exemestane + IMC-A12 was 13 months (HR = 0.77). We assumed that the average time between progression and death from disease was 12 months (95% CI: 6, 18 months) (1), which corresponds to the relationship in treatment effects between PFS and OS endpoints from a recent meta-analysis of 67 trials in metastatic breast cancer(2).

Utilities: The mean health state utility value for stable metastatic breast cancer was 0.76 (95% CI: 0.72, 0.81), decreasing to 0.59 (95% CI: 0.52, 0.66) after progression. These values were derived from a recent systematic review and meta-analysis of utility values in breast cancer from 49 studies(3).

Treatment costs: IMC-A12 (cixutumumab) is an investigational drug and does not yet have a market price; we therefore did not report VOI estimates including costs.

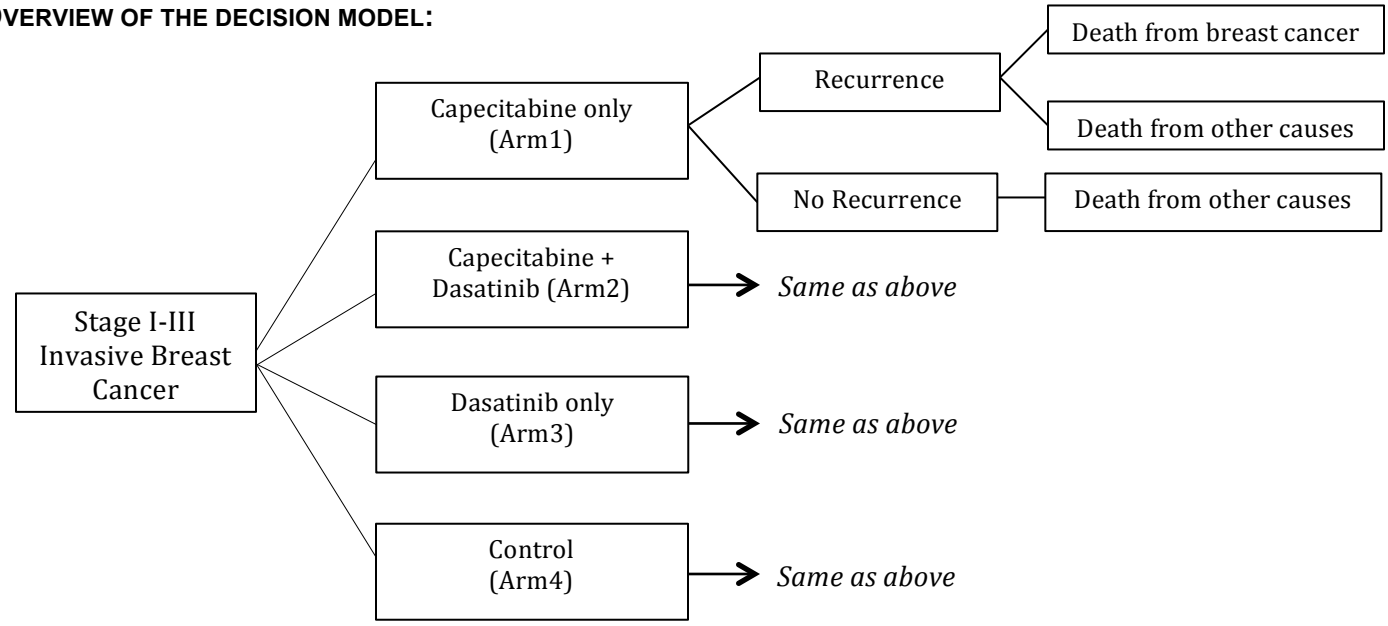
Population projection: Approximately 50,000 women are diagnosed with metastatic breast cancer each year (10,000 as *de novo* stage IV and 40,000 diagnosed as an earlier stage that has recurred) of which ~75% are expected to be ER/PgR positive for a total of 37,500 women each year who are expected to face the treatment decision being evaluated in this trial proposal(4-6). In our simulations we assumed that all women with hormone receptor positive metastatic breast cancer would receive exemestane with or without IMC-A12. The population VOI will be lower if there are other similar treatments available to this patient population that would reduce the use of exemestane and/or IMC-A12.

SUMMARY OF VOI RESULTS:

The expected health benefit of acquiring additional evidence for the decision between exemestane or exemestane + IMC-A12 in metastatic ER/PgR positive breast cancer with this trial proposal is approximately 0.48 quality-adjusted life years (QALYs) per individual who faces the decision. If we monetize health benefits at $100,000 per QALY, this is equivalent to $48,100, which is the clinical VOI. Taking into account the number of individuals who will face this decision in the near to immediate future, the population-level clinical VOI is approximately $6.6 billion.

A PHASE III STUDY EVALUATING THE EFFICACY OF CAPECITABINE AND DASATINIB AS ADJUVANT THERAPY IN PATIENTS WITH HER-2/NEU NEGATIVE BREAST CANCER AND RESIDUAL INVASIVE DISEASE AFTER NEOADJUVANT ANTHRACYCLINE AND TAXANE-BASED CHEMOTHERAPY

OVERVIEW OF THE DECISION MODEL:



SUMMARY OF MODELING INPUTS:

PARAMETER	VALUE	SOURCE
TRIAL INPUTS		
Length of accrual + follow up	7 years	Capsule
Sample size	720	Capsule
DECISION MODEL INPUTS		
5-year DFS in control arm	61%	Capsule
Hypothesized 5-year DFS with Capecitabine OR Dasatinib	72%	Capsule
Hypothesized 5-year DFS with Capecitabine + Dasatinib (Arm 2)	80%	Capsule
Probability Capecitabine OR Dasatinib is superior to control	60%	Assumption
Probability Capecitabine OR Dasatinib is significantly superior to control	25%	Assumption
Utility, stable early stage breast cancer	0.73	(3)
Utility, recurrence of early stage breast cancer	0.68	(3)
Average time between recurrence and death	2 years	(7, 8)
Average age of patient population at enrollment	60	Assumption
Annual treatment costs for stable early stage breast cancer	$3400	(9)
Annual treatment costs after recurrence of early stage breast cancer	$34,000	(9)
Cost, capecitabine (per protocol)	$10,300	(10)
Cost, dasatinib (per protocol)	$29,400	(10)
POPULATION PROJECTION INPUTS		
Number affected individuals per year	69,200	SEER, (11)
Time horizon for information	10 years	Assumption

VALUE OF INFORMATION (VOI) RESULTS:

	PER PATIENT WHO FACES DECISION	ENTIRE PATIENT POPULATION
CLINICAL VOI	$25,800	$4.3 billion
VOI	$2600	$426 million

EXPLANATION OF MODELING INPUTS:

Decision model: The decision model schematic represents the key health states through which patients move in the model. For this decision model, women with stage I-III invasive breast cancer can receive capecitabine, dasatinib, neither (control), or both after which they can experience a recurrence and ultimately die from breast cancer or other causes.

Health state transitions: The 5-year disease-free survival (DFS) for the control arm was 61% based on data presented in the capsule. Under the alternative hypotheses, the 5-year DFS for capecitabine or dasatinib was 72%. We assumed that the average time between recurrence and death from disease was 2 years (95% CI: 1, 3) (7, 8) as prior studies indicate a robust relationship between DFS and OS in early breast cancer(12, 13).

Utilities: The mean health state utility value for pre-recurrence health states was 0.725 (95% CI: 0.668, 0.782), decreasing to 0.684 (95% CI: 0.653, 0.714) post-recurrence(3). These values were derived from a recent systematic review and meta-analysis of utility values in breast cancer from 49 studies(3).

Treatment costs: We assumed that the annual ongoing costs for patients who had not experienced a recurrence were $3400, increasing to $34,000 after a recurrence(9). We calculated the cost of protocol-related treatment for each arm using average drug prices from an online pharmacy database(10).

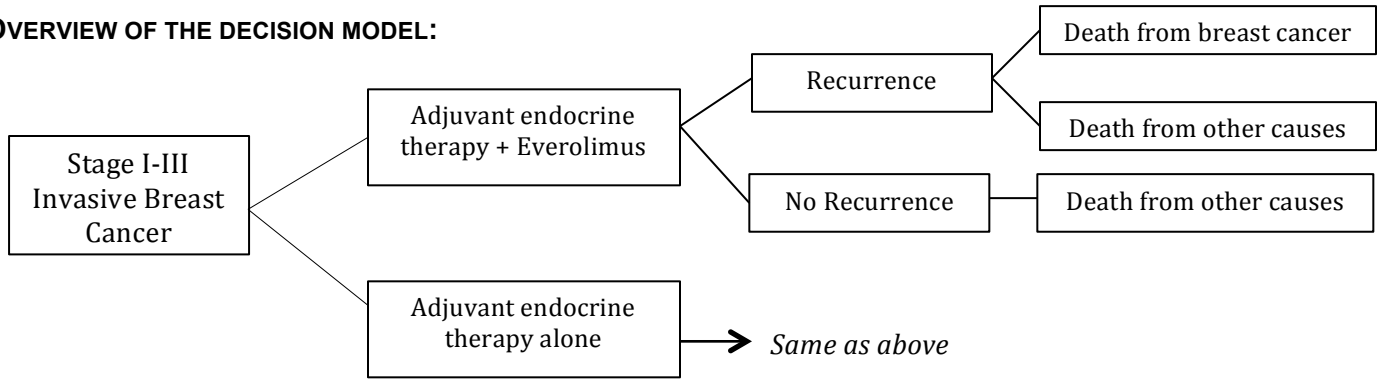
Population projection: Approximately 215,000 women are diagnosed with non-metastatic breast cancer each year, of whom 40% are expected have residual disease or positive lymph nodes after surgery and ~80% are expected to be HER-2 negative, for a total of 69,200 women each year who would potentially face the treatment decision being investigated by this trial(6, 11).

SUMMARY OF VOI RESULTS:

The expected health benefits of acquiring additional evidence for the decision between capecitabine and/or dasatinib with this trial proposal is approximately 0.26 quality-adjusted life years (QALYs) per individual who faces the decision. If we monetize health benefits at $100,000 per QALY, this is equivalent to $25,800, which is the per-patient clinical VOI. If we include the costs of treatment, the VOI of acquiring additional evidence is $2600 per individual who faces the decision. The VOI is lower than the clinical VOI because the potential clinical benefit comes at a substantial increase in treatment costs. Taking into account the number of individuals who will face this decision in the near to immediate future (10 years), the clinical VOI is approximately $4.3 billion and the net present VOI is $426 million.

PHASE III RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL EVALUATING THE USE OF ADJUVANT ENDOCRINE THERAPY +/- EVEROLIMUS IN PATIENTS WITH HIGH-RISK, NODE-POSITIVE, HORMONE RECEPTOR POSITIVE AND HER2-NEU NORMAL BREAST CANCER

OVERVIEW OF THE DECISION MODEL:



SUMMARY OF MODELING INPUTS:

PARAMETER	VALUE	SOURCE
TRIAL INPUTS		
Length of accrual + follow up	6 years	Capsule
Sample size	3400	Capsule
DECISION MODEL INPUTS		
5-year DFS with adjuvant endocrine therapy alone	80%	Capsule
Hypothesized 5-year DFS with Everolimus	84.6%	Capsule
Probability Everolimus is superior to adjuvant endocrine therapy alone	60%	Assumption
Probability Everolimus is significantly superior to adjuvant endocrine therapy alone	25%	Assumption
Utility, stable early stage breast cancer	0.73	(3)
Utility, recurrence of early stage breast cancer	0.68	(3)
Average time between recurrence and death	2 years	(7, 8)
Average age of patient population at enrollment	60	Assumption
Annual treatment costs of stable early stage breast cancer	$3400	(9)
Annual treatment costs after recurrence of early stage breast cancer	$34,000	(9)
Annual cost of everolimus (per protocol)	$97,500	(10)
POPULATION PROJECTION INPUTS		
Number affected individuals per year	21,500	SEER, (11)
Time horizon for information	10 years	Assumption

VALUE OF INFORMATION (VOI) RESULTS:

	PER PATIENT WHO FACES DECISION	ENTIRE PATIENT POPULATION
CLINICAL VOI	$30,200	$2.1 billion
VOI	$5400	$370 million

EXPLANATION OF MODELING INPUTS:

Decision model: The decision model schematic represents the key health states through which patients move in the model. For this decision model, women with stage I-III invasive breast cancer can receive adjuvant endocrine therapy alone or adjuvant endocrine therapy + exemestane after which they can experience a recurrence and ultimately die from breast cancer or other causes.

Health state transitions: The 5-year disease-free survival (DFS) for the adjuvant endocrine therapy alone arm was 80% based on data presented in the capsule. Under the alternative hypotheses, the 5-year DFS with was 84.6%. We assumed that the average time between recurrence and death from disease was 2 years (95% CI: 1, 3) (7, 8) as prior studies indicate a robust relationship between DFS and OS in early breast cancer(12, 13).

Utilities: The mean health state utility value for pre-recurrence health states was 0.725 (95% CI: 0.668, 0.782), decreasing to 0.684 (95% CI: 0.653, 0.714) post-recurrence(3). These values were derived from a recent systematic review and meta-analysis of utility values in breast cancer from 49 studies(3).

Treatment costs: We assumed that the annual ongoing costs for patients who had not experienced a recurrence were $3400, increasing to $34,000 after a recurrence(9). We calculated the cost of protocol-related treatment for each arm using average drug prices from an online pharmacy database(10).

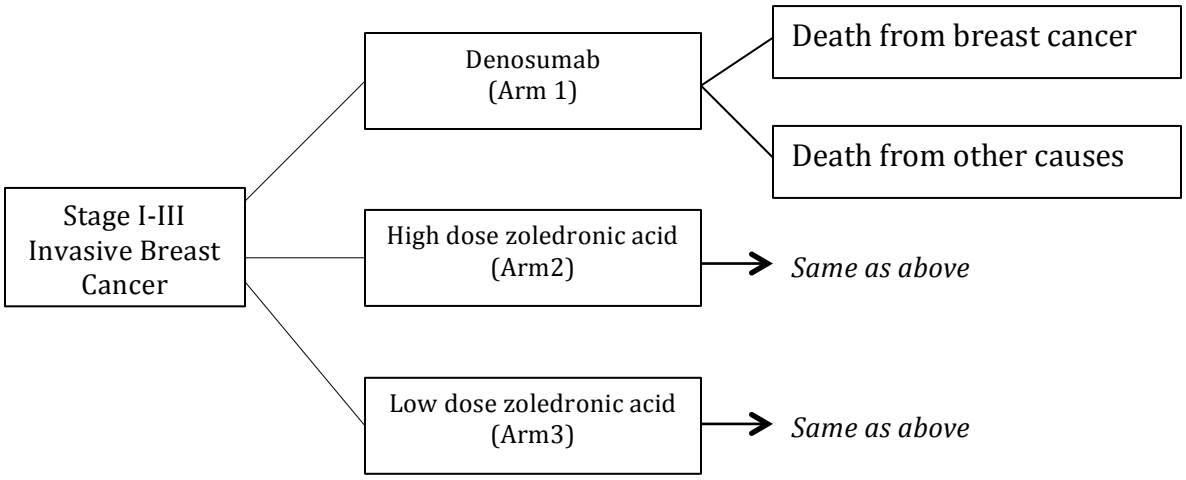
Population projection: Approximately 215,000 women are diagnosed with non-metastatic breast cancer each year, of whom 10% are expected to be high-risk, node positive, hormone receptor positive and HER2-neu normal (~15,000 with 1-3 nodes and RS>25 and 6500 with 4+ nodes, according to data presented in this and the RxPonder protocols), for a total of 21,500 women each year who would potentially face the treatment decision being investigated by this trial(6, 11).

SUMMARY OF VOI RESULTS:

The expected health benefits of acquiring additional evidence for the decision between adjuvant endocrine therapy alone or in combination with everolimus is approximately 0.30 quality-adjusted life years (QALYs) per individual who faces the decision. If we monetize health benefits at $100,000 per QALY, this is equivalent to $30,200, which is the per-patient clinical VOI. If we include the costs of treatment, the net present value of acquiring additional evidence is $5400 per individual who faces the decision. The VOI is lower than the clinical VOI because the potential clinical benefit comes at a substantial increase in treatment costs. Taking into account the number of individuals who will face this decision in the near to immediate future (10 years), the clinical VOI is approximately $2.1 billion and the net present VOI is $370 million.

PHASE III TRIAL TO EVALUATE INTENSIVE VS. LESS INTENSIVE DOSING OF ZOLEDRONIC ACID VS. DENOSUMAB AS ADJUVANT THERAPY FOR EARLY STAGE BREAST CANCER

OVERVIEW OF THE DECISION MODEL:



VOI FEASIBILITY ASSESSMENT:

The primary endpoint of the proposed trial was overall survival, however, there are expected to be important differences in quality of life and rates of adverse events between the treatment alternatives. These outcomes are not likely captured in the primary endpoint of the trial, and sufficient data on the expected outcomes for quality of life measures were not provided in the capsule to either derive a prior distribution of treatment effect or easily extrapolate from these outcomes to differences in quality-adjusted life years. Due to these limitations it will not be feasible to calculate VOI using our "minimal modeling" framework for this capsule.

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KEY ASSUMPTIONS USED IN ALL VOI CALCULATIONS

- Probability of Trial Success
  - Assume there is a **25% chance the experimental treatment is significantly superior** (or non-inferior) to the standard treatment and a **60% chance that the new treatment was superior** to the standard treatment. Over the last 50 years, ~25% of NCI-cooperative group trials have found a statistically significant result in favor of the experimental treatment and ~60% of NCI-cooperative group trials favored the experimental treatment.
  - Assume that all trial proposals included in this historical analysis had the **same chance of success**. We will also determine the probability of success for each trial proposal individually using **expert opinion** when these analyses are conducted prospectively.
- 10-Year Time Horizon for Information
  - Assume a 10-year effective lifetime of the information generated by the trial. In other words, the results from the trial remain relevant to patients and providers for 10 years. The future is complex and uncertain: after 10 years we assume that newer technologies are available, the size of the patient population has changed, and/or that other evidence is available, which makes VOI projections beyond 10 years difficult.
  - We calculate the expected health outcomes and treatment costs over a lifetime for all patients predicted to be treated within the 10-year time horizon. These are discounted at 3% annually, following convention in health economic evaluations.