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Simulating the contribution of a biospecimen and clinical data repository in a phase II clinical trial: a value of information analysis

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Abstract

The potential contributions of a centralized data warehouse or repository in clinical research include the expedited accrual of subjects for phase II trials. Understanding the contribution of data warehouses that integrate clinical, biospecimen, and molecular data for the conduct of clinical trials is essential to inform private and public decisions on resource allocation and investment.

We conducted a value of information analysis using data from recent trials at the Moffitt Cancer Center and simulated the potential reductions in trial size due to possible alternative scenarios of expedited accrual. In this study, we compared alternative data sets using a single model to assess VOI. Our findings suggest that the reductions in trial size range from 0% to 43%, depending on the amount of censoring in overall survival. The ability to expedite the accrual of patients for clinical trial studies using large data repositories that store data on inclusion/exclusion criteria and response to standard of care therapies demonstrated significant improvement in reducing the number of subjects needed to achieve similar end-results, as evaluated using VOI analysis with a limited number of parameters and a parsimonious model of OS.

Keywords

value of information; clinical trials; phase II; neoplasms; biorepository

INTRODUCTION

Efforts in the discovery of biomarkers for early detection of disease or for the identification of genetic signatures to guide optimal treatment selection have resulted in numerous large

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Conflict of Interest Statement

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collections of tissue, serum, plasma, blood, and buccal swabs.(1) Most biorepositories were established simply to store biological samples from a specific study or group of studies.(2) Few institutions have established the infrastructure necessary for the systematic collection and maintenance of samples, related molecular analyses, electronic medical records, and other data from patient populations.(3, 4) By taking a system approach, biomarker and genetic profile information not only enables personalized medicine for a patient population, but promotes comparative effectiveness research (CER). Understanding the contribution of data warehouses that integrate clinical, biospecimen, and molecular data for the conduct of clinical trials is essential to inform private and public decisions on resource allocation and investment.

Biorepositories have recently been both praised and condemned by funding organizations and the media.(5, 6) With personalized medicine on the horizon, the National Institutes of Health (NIH) invested heavily in the development of information and biospecimen infrastructures through internal projects (e.g., caBIG[®], Cancer Genome Atlas), institutional awards, and sponsored projects.(7) In 2006, the National Cancer Institute's (NCI) Office of Biorepositories and Biospecimen Research (OBBR) initiated the Biospecimen Research Network "to coordinate and support systematic investigation into how collection, processing, and storage of human biospecimens affect subsequent molecular analysis."(8, 9) In 2009, OBBR received 60 million dollars from the American Recovery and Reinvestment Act (ARRA) to create the Cancer Human Biobank (caHUB), a national biospecimen initiative. (10) While the productivity of these initiatives has been criticized, their purpose to establish a biorepository infrastructure remains of great interest.

Scientists espouse the benefits of data centralization, potentially funded through governmental support; (11, 12) however, its cost, both financial and privacy risks, must be balanced against the value of potential contributions. How might a centralized system allow private investment, address ethical and legal concerns about governmental genetic registration, and facilitate innovation in biobanking technologies?(13–16) These questions are currently being debated at the federal level while grassroots initiatives have established large regional biospecimen and clinical data repositories.

In 2003, the Moffitt Cancer Center (MCC) began developing Total Cancer Care[™] (TCC), which is a holistic plan to improve the standard of care by combining information technology, science, and clinical treatment. This systematic approach will provide evidence-based guidelines to improve care and outcomes for cancer patients throughout the state of Florida and beyond. TCC addresses cancer as a public health issue, following the patient through the continuum of screening and genetic predispositions, diagnosis, treatment, and survivorship. What makes TCC more than just a registry, cohort study, and tissue bank is the added value of integrating the collection, and storage of tissue and information on a large scale. TCC includes prospectively consenting patients for collecting tissue, collecting clinical data throughout a patient's lifetime, utilizing electronic data capture processes, molecularly characterizing tumors, data integration using a multi-dimensional data warehouse, and designing different views to the data for the patients, clinicians, and researchers. Translational research is incorporated at each step along this continuum of care.

Along with the collection and storage of a very large amount of samples and information that facilitate in-depth analyses, biorepositories can facilitate clinical trials in a variety of ways, by (1) expediting the accrual of trial participants (i.e., loading); (2) collecting samples and data before, during, and after trial accrual; (3) improving the standardization and randomization of trial protocols; (4) curating, maintaining, and protecting patient data; and (5) facilitating collaborative access to data and appropriate analytical tools—all of which may enable trials to end earlier and involve fewer participants, thus having scientific, economic, and ethical advantages.

The benefits of a regional biospecimen and clinical data repository may be most evident for phase II clinical trials, because these trials are smaller and typically conducted at a single site. Within the near future, phase II trial patient accrual may be expedited using the TCC data warehouse to contact and recruit potential participants at the initiation of the trial, as well as an avenue to promote access to state-of-the-science medicine.

In this paper, we examine one potential contribution of such a critical resource to translational research. We also examine the value of expedited participant accrual (value of information [VOI]) using existing data from 11 published investigator-initiated, pre-TCC, phase II trials that were conducted at MCC from 2000 to 2010. In this VOI study, we measure value in terms of potential reductions in sample size, not in monetary terms (i.e., reduced cost of trial). For each of the 11 pre-TCC trials, this VOI analysis simulates how many subjects are required to attain an equal amount of information as at baseline in a real-world setting.

METHODS

Empirical analyses typically assess goodness-of-fit by comparing alternative model specifications using a single data set. In this study, we compare alternative data sets using a single model to assess VOI. Specifically, we focus on 2 attributes of trial data: number of subjects (N) and number of subjects accrued at trial initiation (L N). Phase II clinical trials vary by design (e.g., target population, number of subjects, length of follow-up) and by simulating an increased accrual; we hypothesize, in general, that fewer subjects would be required to achieve the same information. Such simulations are conducted both for the studied data sets and generated data.

Value of Information Analysis

Within the statistical literature there are different approaches on how to select a model among a set of competing models that best describes a data set. Regardless of criterion used to rank models in terms of goodness-of-fit, these entropy measures could be considered potential candidates in evaluating the VOI contained in the alternative data sets using the same model. Specifically, this analysis of overall survival (OS) utilizes information criteria commonly used for model selection in order to quantify the value of information added to data with increased accrual.

Most entropy measures are based on the aggregate log-likelihood (LL) of observing a dataset, assuming it is generated by a specific model. In this study, the LL for OS incorporates censoring under the assumption of an exponential distribution, i.e.,

$$LL = \sum_{i=1}^N (y_i \leq Y_i) (\ln(\lambda) - \lambda y_i) + (y_i > Y_i) \ln(1 - \exp(-\lambda Y_i)),$$

where y_i is the i^{th} subject's time from accrual to death, and Y_i is the i^{th} subject's time from accrual to last follow-up visit. This single-parameter model is a parsimonious specification that may be expanded in future research examining the tradeoffs between sample size and censoring.

We use 2 entropy measures, Bayesian information criterion (BIC) and Akaike information criteria (AIC) to compare models. BIC is defined as $-2LL + k \ln(N)$, where k is the number of parameters. BIC has been established to be asymptotically related to Bayes factors commonly used for model selection for large numbers of observations.⁽¹⁷⁾ Estimation of such Bayes factors would directly involve estimation of integrals with no closed form solutions. The alternative classical entropy measure, Akaike information criteria (AIC), is defined as $-2LL + 2k$. Unlike BIC, AIC does not penalize for number of parameters as much as BIC and strikes an arbitrary trade-off between bias and variance within a frequentist framework. As a tool for model selection, neither of the 2 criteria may be appropriate in small samples, particularly because simply adding parameters can increase both AIC and BIC. However, as measures of entropy, both BIC and AIC increase with larger samples and were applied to the phase II trial data and simulations.

Phase II Trial Data

Through the design of a phase II trial, MCC researchers had some control over their data structure in terms of the amount of censoring and number of observations. To better understand the contribution of the TCC data warehouse that includes biorespository data for a phase II clinical trial, our study estimates OS using a simple exponential model and secondary data from the 11 phase II trials. (18–28) Multi-site and unpublished studies were excluded from this analysis due to data sharing considerations. One study examined only progression-free survival and was excluded.⁽²⁹⁾ Unlike the term progression-free survival, identical definitions of OS (time from consent to last follow-up or death) were included in all studies, and OS is the primary endpoint for these analyses.

These studies represent the diversity of research interests at MCC (Table 1). The fundamental characteristics of a phase II clinical trial can be summarized using 5 parameters:

N: number of subjects

OS: expected overall survival

T: trial duration

A: minimum amount of follow-up after accrual

L: loading, percentage of individuals accrued through the TCC data warehouse at initiation

Five studies included non-small cell lung cancer patients with sample sizes ranging from 40 to 62.(19) One studied melanoma patients with a sample size of 24 and another carcinoma with sample size 32.(22) Romero and colleagues studied prostate cancer with a sample size of 39. (26) Given that all studies were initiated prior to TCC, no patients were accrued through the data warehouse at the beginning of the study ($L=0$). BIC and AIC were estimated using the trial datasets (Table 2).

Three NOSTALGIA Simulations

Because biospecimen and clinical data repositories are largely motivated for Genetic Information Analysis (GIA) and because this investigation looked retrospectively at past phase II trials to imagine what could have been, these simulations are represented by the acronym: NOSTALGIA. In addition to the trial parameters (N , OS , T , A , and L) and the exponential distribution of OS , we assumed that the non-loaded subjects, $N \times (1-L)$, accrued at a constant rate over the period from trial initiation to the end of accrual, $T-A$. This conservative assumption implies that increased loading lowers the accrual rate, $(T-A)/(N \times (1-L))$. We experimented with other accrual rate specifications for non-loaded subjects, but these specifications did not substantially change the results.

For each simulation, a data set was generated according to the assumed model and then the parameters of interest were estimated. The first NOSTALGIA simulations predicted the median BIC and AIC estimates (Table 2) given the trial characteristics (Table 1). Monte Carlo experiments of each of the 11 trial characteristics resulted in 1000 random samples. Like with the actual data, BIC and AIC were estimated for each simulation. For every set of 1000 BIC and AIC estimates, medians were computed. The concordance between the actual BIC/AIC and simulated medians reflected the convergent validity of the NOSTALGIA simulations. Differences may be attributed to randomness or discordance with the assumption of an exponential survival distribution and constant accrual, although the simulation results are in line with the estimated parameters.

The second set of NOSTALGIA simulation examined the effects of greater loading ($L > 0\%$) For each set of trial characteristics (Table 1), loading (L) was increased from 0% to 100% in 1 person units. The effect of loading is expressed by the change in LL, which is translated into the number of subjects needed to achieve the same LL increase. Trials, where loading had no effect due to lengthy follow-ups (i.e., no censoring at $L=0$; $OS < A$), were not included in this analysis. The amount of loading needed to achieve a change in LL equal to 1 additional subject is shown in Table 2 by trial.

In the third set of simulations, we examined a fuller array of trial parameters, varying N from 25 to 70 by 5; OS from 6 to 72 by 6; T from 36 to 72 by 6; and A from 6 to 48 by 6. These values were selected to cover the full spectrum of trial characteristics consistent with the 11 studies. OS was constrained to be between one-third and 3 times the minimum follow-up time after accrual to allow a moderate amount of censoring. For each simulation,

we estimated the potential reduction in trial size needed to achieve the same information criteria if trials were switched from no loading ($L=0\%$) to fully loaded ($L=100\%$). The BIC and AIC median results were nearly identical and are illustrated (Figures 1 and 2) with respect to rescaled minimum follow-up time, A/OS , and trial length T/OS .

RESULTS

Table 2 lists the AIC and BIC estimates from the 11 clinical trials and the median estimates from the NOSTALGIA simulations having the same settings of (N , OS , T , A , L). Paired AIC and BIC values were nearly identical. The simulated median AIC and BIC were comparable to the AIC and BIC estimates, and a larger sample size corresponded to a higher discrepancy between the simulated and the estimated criteria. The problem with such discrepancies could potentially be addressed by alternative distributional assumptions on the data generating process including 2 and 3 parameter distributions.

After translating the effects of loading on LL for the 11 trials, we found that 3 trials would not have benefited from increased loading, either because there was no censoring (Trials 3 and 4; i.e., A is large) (20, 21) or because subjects died quickly relative to A (Trial 1). (18) The trial most likely to benefit from loading had an OS of 22.99 months and a minimum follow-up time from accrual to last follow-up of 3.78 months (Trial 10).(27) In this best-case scenario, loading its participants ($L=100\%$) would have allowed a decrease in trial size from 53 to 22 participants (40% decrease).

Figure 1 illustrates the potential effects of 100% loading based on the ratio of minimum follow-up time and overall survival (A/OS). Within these parameter ranges, the effect of loading was between 2% and 43%, similar to the second NOSTALGIA simulations. As minimum follow-up time increased as a fraction of OS , the effect of loading increased due to increased censoring. Figure 2 examines the 2 scenarios: $A=OS/2$ and $A=OS$, where loading had a substantial effect. Under both specifications, the loading effect increased and decreased with rescaled trial length. Generally, when a trial was short ($T/OS < 2$), increasing trial length increased the amount of information gained from loaded subjects almost linearly. When a trial was long, ($T/OS > 3$), increasing trial length diminishes the loading effect, because it reduced censoring of OS . The actual OS and sample size had little to no influence of the loading effect compared to A/OS and T/OS . In fact, the reduction in the trial size was maximized when $T/OS=2$.

DISCUSSION

We found that loading had an additive effect on the AIC and BIC criteria (i.e., changes in LL), which suggested that its benefits may be interpreted as either an increase or decrease in sample size. For example, if the last trial listed in Table 2 (28) had loaded 12% of its subject, it could have decreased its sample size by 1 subject or benefited from an additional subject's worth of information in its OS analysis. In the best-case scenario (27), loading half of the subjects would have allowed a 20% drop in sample size without loss of information, which represented an appreciable saving in trial costs and patient burden.

The benefits of loading depend on the amount of censoring in a phase II trial. In cases where minimum follow-up time with respect to survival is short (A/OS), loading may have a large effect, up to 40% reduction in trial size. The effect of loading also depended on the trial length, T/OS, but varied little on sample size and OS. We also estimated a non-linear regression based on T/OS and A/OS to predict the potential gains from 100% loading ($R^2=0.98$):

$$\text{Potential reduction} = 0.9712 - 0.1923 \cdot \text{OS}/T - 0.2075 \cdot T/\text{OS} + 0.0149 \cdot (T/\text{OS})^2 + \text{A}/\text{OS} \cdot (-0.3132 - 0.4132 \cdot \text{OS}/T + 0.1091 \cdot T/\text{OS} - 0.0104 \cdot (T/\text{OS})^2)$$

By inserting rescaled trial length and minimum follow-up times into this formula, trialists can predict the potential reduction in trial size due to loading. These simulations may help trialists in their decisions about the value of a biospecimen and clinical data repository.

Loading also has the potential risk of “gaming” the selection of patients. With in-depth information on each patient, trialists may prefer selection criteria based on patient availability or on patients with poor response to standard of care. This bias is present without loading but on an aggregate level. Technological advances, such as loading, will require new forms of administrative oversight to optimize their benefits, including standardized recruitment criteria.

This simulation analyses focused on only one potential contribution of a biospecimen and clinical data repository (i.e., reduced number of trial subjects) and OS under the exponential assumption. Other benefits of loading include the potential to end trials earlier, which has scientific and economic advantages. In such analysis the cost of time would need to be explicitly modeled. More complicated simulations may incorporate more flexible distributions (e.g., piecewise exponential survivals) and test for subgroup effects. Expedited accrual also has potential benefits for phase III clinical trials, which may be conducted over multiple centers and heterogeneous populations. Still, the primary motivation for this study was to simulate one of the primary contributions of data warehouse in a phase II clinical trials.

The future of molecularly based personalized medicine will uncover new innovations as the identification of molecular signatures for diagnosis, prognosis, and prediction of response to therapy add to the body of information available for designing clinical trials. Within the realm of cancer research, several drugs have specifically targeted biomarkers, such as Gleevec (Imatinib) for the treatment of chronic myeloid leukemia (CML) (30) and Herceptin (Trastuzumab) for Her-2 over expression in breast cancer (31). The variability in the failure to respond to standard drug therapies ranges from 30%–70% and may be due to many factors, whereas molecular targeted therapies may have positive outcomes in fewer patients; Her-2 is only elevated in approximately 20% of invasive breast cancers (32). To effectively assess new molecular-targeted therapies in cancer the need for molecular analyses of tumors, by resection or biopsy, will be an essential part of the design of stratified clinical trial designs as trials become smaller, shorter, cheaper, and more individualized (33). It is evident that the development of new molecularly targeted treatments will also require the use of clinical, molecular, and biospecimen data generated from the point of care.

In addition to targeted accrual, these data may be linked to other forms of observational data including surveillance data from cancer registries and CMS (Centers for Medicare and Medicaid Services) data, which aid the design of clinical trials and comparative effectiveness research studies, strengthening the ability to learn more about the subgroups of patients who benefit from specific therapies and influence the design of targeted validation studies (34, 35). The sheer volume and complexity of patient data that will be available electronically in the near future will require novel data management strategies that allow researchers to evaluate the value and usability of the data for specific applications.

Total Cancer Care (TCC) is a prospective study and translational research plan created to evaluate how patient-level data can be used to promote personalized medicine. So far, more than 75,000 cancer patients have consented to: 1) be contacted throughout their lives about the health and care; 2) contribute tissue samples for research that will molecularly characterize cancer diseases, personalize cancer care and treatment, and reveal targets that can be exploited for the development of new treatments; and 3) release de-identified medical history data to be used for research. The creation of a state-of-the-art data warehouse that combines patients' clinical data with information about the molecular characteristics of the resected/biopsied tumors and outcomes data is essential to creating infrastructure to support personalized medicine and translational research. The integration of numerous source data systems including electronic medical records (EMR), a biorepository, a cancer registry, and molecular databases is revealing new opportunities to repurpose these data for comparative effectiveness research and to augment the conduct of clinical trials as examples.

In this manuscript, the ability to expedite the accrual of patients for clinical trial studies using large data repositories that store data on inclusion/exclusion criteria and response to standard of care therapies demonstrated significant improvement in reducing the number of subjects needed to achieve similar end-results, as evaluated using VOI analysis with a limited number of parameters and a parsimonious model of OS. The knowledge generated by this and other studies currently underway at the MCC is providing the foundation for creating the next generation of data management infrastructure to support personalized molecular medicine. As these resources mature, the assessment of the data using various analysis strategies, such as VOI, will be imperative to understand how these data can be leveraged to enhance patient care and improve treatment outcomes based on evidence-based guidelines.

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Figure 1.
Potential Reduction in Trial Size due to Loading by Minimum Follow-up Time (A/OS)

Figure 2.
Potential Reduction in Sample Size due to Loading by Trial Length divided by Overall Survival

Table 1

Characteristics of 11 phase II clinical trials conducted at Moffitt Cancer Center

Trials	Cancer Site	N	OS	T	A
1. Antonia et al., 2006	small-cell lung	36	16.79	50.38	7.93
2. Bepler et al., 2008	non-small-cell lung	52	71.50	50.94	26.25
3. Chiappori et al., 2005	non-small-cell lung	40	14.05	91.97	77.39
4. Chiappori et al., 2008	non-small-cell lung	44	14.86	69.29	45.42
5. Daud et al., 2009	melanoma	24	14.00	27.44	1.06
6. Fishman et al., 2008	renal cell	32	4.44	41.55	4.17
7. Moulder et al., 2008	breast	52	15.50	52.43	23.60
8. Ramnath et al., 2005	non-small-cell lung	62	56.75	98.38	55.34
9. Romero et al., 2007	prostate	39	10.40	48.66	15.97
10. Simon et al., 2007	non-small-cell lung	53	22.99	62.67	3.78
11. Simon et al., 2008	non-small-cell lung	49	18.11	66.92	19.00

Abbreviations: N, Number of Subjects; OS, Expected Overall Survival in Months; T, Trial Duration in Month; A, Minimum Time from Accrual to Last Follow-up Visit in Month.

Table 2

Estimated and Simulated Information Criteria for Overall Survival Analysis

		Estimated		Simulated Median		Simulated Gain from Loading	
		BIC	AIC	BIC	AIC	%*	%
1.	Antonia et al., 2006	241	240	191	190	>100%**	>100%**
2.	Bepler et al., 2008	158	156	176	174	15%	15%
3.	Chiappori et al., 2005	253	252	294	292	>100%**	>100%**
4.	Chiappori et al., 2008	286	284	314	312	>100%**	>100%**
5.	Daud et al., 2009	112	111	90	89	19%	19%
6.	Fishman et al., 2008	158	156	149	147	36%	36%
7.	Moulder et al., 2008	336	334	329	327	17%	17%
8.	Ramnath et al., 2005	296	294	403	401	10%	10%
9.	Romero et al., 2007	177	175	233	232	25%	25%
10.	Simon et al., 2007	353	351	279	277	5%	5%
11.	Simon et al., 2008	291	289	312	310	12%	12%

* Gain of loading is expressed as the percentage of loading needed to attain information equal to 1 additional subject.

** The simulations found no expected gain for loading at L=100% due to a lack of censoring in the original trial design.

Abbreviations: BIC, Bayesian Information Criterion; AIC, Akaike Information Criterion