

# Development of a Charter for an Endpoint Assessment and Adjudication Committee

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*The significant programmatic risk inherent in a decision to advance a product candidate to a late phase of clinical development can be significantly reduced when there is complete objectivity in the data assessment and analysis underlying the decision to proceed in development. Such objectivity is especially needed in fields in which endpoints are determined by clinical or radiological examinations, rather than by pre-defined laboratory measurements. A charter for an independent Endpoint Assessment and Adjudication Committee was developed for the unbiased assessment of clinical outcomes in a multicenter, phase 3 oncology trial to enable a uniform, controlled-assessment process that*

*would be independent of the sponsor. The Endpoint Assessment and Adjudication Committee charter enabled objectivity of endpoint assessment and approximated the critical review that the U.S. Food and Drug Administration (FDA) might impose on clinical endpoint data. The Endpoint Assessment and Adjudication Committee charter was reviewed rigorously in consultation with the FDA, resulting in a charter that may prove to be a useful example in generating independent assessment of pivotal clinical outcomes. The Endpoint Assessment and Adjudication Committee charter is available for review at <http://www.vical.com/eaaccharter.pdf>.*

## Key Words

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## INTRODUCTION

### IMPORTANCE OF OBJECTIVE CONCLUSIONS FROM CLINICAL RESEARCH

The importance of reaching objective and definitive conclusions from clinical research and development is essential to clinical drug development. Completely excluding bias during this process is of critical importance. The lessons learned by sponsors (1) whose pivotal trial data were found not to support the conclusions set forth in a license application can reveal experiences that are best not repeated. While the critical decision to advance a product candidate to a very late phase of clinical development carries significant business risk, that risk is reduced when there is real objectivity in the interpretation of the data underlying the decision to proceed in development.

Vical Incorporated completed a pivotal, multicenter, phase 3 trial of an immunotherapeutic product in a metastatic melanoma population. In an effort to increase the accuracy of the study's conclusions and eliminate bias, Vical collaborated with the U.S. Food and Drug Administration (FDA) and a state-of-the-art bio-imaging

enterprise to develop a charter for an Endpoint Assessment and Adjudication Committee. This paper describes the development of the Endpoint Assessment and Adjudication Committee charter and summarizes its features, which may make it a useful model for the industry.

### OPERATIONAL CHALLENGES TO ACCURATE AND BIAS-FREE CONCLUSIONS FROM ONCOLOGY TRIALS

Deriving accurate and bias-free conclusions from clinical trials in oncology is a well-known complex operational challenge. Maintaining and following Good Clinical Practice guidelines as well as other guidance documents is required throughout and is especially important in trials supporting product registration (2). This is particularly difficult when response rates are based on clinical criteria such as physical and radiological examinations rather than based on validated, precise, and accurate laboratory tests.

Clinical trials used to support registration require an operational rigor of conduct, including a planned exclusion of bias which is above reproach in order to win support for an objective claim of clinical benefit. This operational rigor helps to ensure both the integrity of data and

TABLE 1

Sponsor's Responses to Potential Bias in a Pivotal Clinical Trial	
Potential Bias	Sponsors' Responses
Clinical/medical monitors may become passively familiar with subsets of study data that suggest study outcomes	Segregate study management processes from data handling processes
Investors and interested parties pressure sponsor to look at early endpoint data	Develop statistical analysis plan, and written <i>clinical standard</i> operating procedures that define when and how data may be examined or reported
Assessment of clinical endpoints is especially complex, can vary from assessor to assessor, or is inherently subject to the appearance of bias	Sponsor arranges independent blinded assessment and adjudication of endpoint data by an independent committee of trained assessors for interim and end-of-study analyses

the integrity of the process used to generate, collect, analyze, and report the data.

Sponsors who understand this requirement may take certain steps to exclude potential bias in their management of pivotal trials as well as in their handling of trial data. Table 1 shows some of the ways in which sponsors may respond to a potential for bias in the management of pivotal trials. To help reduce bias and increase accuracy in the assessment of clinical endpoints and outcomes that are observer-dependent, there is a need for a special type of oversight committee. The committee and its work must be designed to maintain blinding, eliminate subjectivity, and define responses as clearly as possible. Such a committee's organization and operation are described in the committee's charter.

#### APPLICABLE REGULATIONS

Federal regulations for clinical trials require sponsors to evaluate study data for safety and efficacy endpoints (3), but currently there are no regulations requiring sponsors to critically assess study outcomes for accuracy or freedom from bias. Nevertheless, the FDA and its federal advisory committees scrutinize the conclusions sponsors present from audited study data in license applications, to ensure that under rigorous clinical and statistical analysis the data do support the study conclusions and the resulting product claims.

An important tool not yet in widespread use in the pharmaceutical and biotechnology industry is the Endpoint Assessment and Adjudication Committee, modeled on the now traditional

Data Monitoring Committee, but with quite a different scope. Vical Incorporated, in close collaboration with the FDA's Center for Biologics Evaluation and Research and Bio-Imaging Technologies Incorporated, has developed a charter for an Endpoint Assessment and Adjudication Committee to determine a truly objective outcome of a pivotal trial in an oncology setting. The charter in its entirety is provided for review at <http://www.vical.com/eaaccharter.pdf>. This paper summarizes important features of the process for developing an Endpoint Assessment and Adjudication Committee charter, which may make it a useful model for clinical research being performed to support registration.

#### THE DATA MONITORING COMMITTEE

A Data Monitoring Committee (DMC) may be defined as a group of independent individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the continuing safety of trial participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial (4).

DMCs initially were used primarily in large, federal-agency-sponsored, multicenter trials that targeted improved survival or reduced risk of major morbidity. Few trials sponsored by the pharmaceutical/medical device industry incorporated DMC oversight until the 1990s. Increasing use of DMCs in industry-sponsored trials is probably due to several factors, including the growing number of industry-sponsored tri-

als with mortality or major morbidity endpoints, increasing collaboration between industry and government in conducting clinical trials under government funding agency policies, and heightened awareness of the potential for inaccurate or biased results in clinical trial conduct and analysis.

The FDA recognizes some other oversight groups, apart from DMCs, which may assume or share responsibility for various aspects of clinical trial monitoring. Such oversight groups, which play different though sometimes overlapping roles, include Institutional Review Boards (IRBs), Clinical Trial Steering Committees, and Endpoint Assessment or Adjudication Committees. While IRB use is mandatory prior to trial initiation, use of the latter three oversight groups has become more prevalent to improve the quality of clinical trial conduct, integrity of data, and analysis of outcomes, whether at interim or final analyses.

Federal regulations require all clinical trials to receive appropriate IRB review and approval, and require all clinical trials to be monitored for safety and compliance to Investigational New Drug application requirements (5). Current FDA regulations, however, impose no requirements for DMCs or endpoint assessment or adjudication committees in clinical trials (6).

The first FDA draft guidance on the application of DMCs appeared in November 2001. The draft guidance (4), entitled *Guidance for Clinical Trial Sponsors—On the Establishment and Operation of Clinical Trial Data Monitoring Committees*, was the subject of an FDA-sponsored workshop (7) that reviewed in detail the history, status, composition, operation, responsibilities, and roles of DMCs. Fleming et al, described the importance of exclusive access to interim efficacy and safety data by the DMC to minimize risk of prejudgment of trial results based on limited data (8). We report here the establishment of an Endpoint Assessment and Adjudication Committee charter based on an understanding of that workshop, on the guidances here referenced, and on our interactions with the Center for Biologics Evaluation and Research (CBER).

## MATERIALS AND METHODS

### THE PIVOTAL PHASE 3 TRIAL DESIGN

A controlled, randomized, multicenter phase 3 trial was conducted in a population of 202 stage III or IV metastatic melanoma patients, to compare the response to dacarbazine (DTIC) alone to DTIC administered in conjunction with a gene-based immunotherapeutic, Allovectin-7®. The study was open label in that subjects and clinical investigators were aware that they were receiving either DTIC alone or DTIC plus Allovectin-7®. The open label nature of the trial was a potential source of introduction of bias, particularly since time to disease progression was a study endpoint.

The phase 3 protocol was the topic of two meetings with CBER's oncology branch: an end-of-phase-2 meeting in 1998 and a follow-up meeting in 2001. Table 2 provides an abstract of the study design.

### STUDY EVALUATION

The protocol required that an independent safety and efficacy committee evaluate response rate and duration and disease progression by measuring tumors identified on the prestudy, end-of-study, and follow-up visit imaging scans. Time to disease progression was measured from day zero to the point at which imaging scan documentation confirmed the occurrence of new tumors or an increase in tumor mass of  $\geq 25\%$  in the sum of the products of the diameters of measurable tumors as compared to baseline measurements. If significant clinical deterioration occurred that could not be attributed to treatment or other medical conditions, an imaging scan was to be performed to document an increase in tumor burden and establish the time point of progressive disease.

The median time to progression, duration of response, and objective response rate were to be calculated for the control group, which received only DTIC. These values would be used as the point of comparison for determining whether the objectives of a two-month increase in median time to disease progression and 15% improvement in rate of response for the group re-

TABLE 2

Protocol Abstract of the Phase 3 Study Design	
<b>Patient Population and Descriptors</b>	
<ul style="list-style-type: none"> <li>• Histologically confirmed stage III or IV malignant melanoma with either a solitary tumor or multiple tumors and at least one metastatic tumor where surgery was not deemed to be a curative option</li> </ul>	
<ul style="list-style-type: none"> <li>• No prior chemotherapy; dacarbazine indicated as first-line chemotherapy</li> </ul>	
<ul style="list-style-type: none"> <li>• Karnofsky performance status of 80% or greater, with life expectancy greater than six months</li> </ul>	
<ul style="list-style-type: none"> <li>• No tumor larger than 100 cm<sup>2</sup></li> </ul>	
<ul style="list-style-type: none"> <li>• Voluntary informed consent</li> </ul>	
<b>Study Drugs</b>	
<ul style="list-style-type: none"> <li>• Dacarbazine given every 4 weeks for a total of 3 cycles in both arms of the study</li> </ul>	
<ul style="list-style-type: none"> <li>• Allovectin-7® ((HLA-B7 /β2-microglobulin) plasmid DNA/lipid complex) given by intratumoral injection on days 3 and 10 of each cycle to patients randomized into Arm Two</li> </ul>	
<b>Objectives</b>	
<ul style="list-style-type: none"> <li>• An improvement in the median time to disease progression of at least two months for patients treated with Allovectin-7®, with no decrease in the rate of objective clinical responses as compared to patients who receive dacarbazine alone</li> </ul>	
Or	
<ul style="list-style-type: none"> <li>• An improvement of at least 15 percentage points in objective clinical responses with no decrease in the median time to disease progression</li> </ul>	
<b>Study Design</b>	
<ul style="list-style-type: none"> <li>• Phase 3, open-label, 2-arm, multicenter, randomized, controlled study, approximately 100 patients per arm in the protocol as amended from the initial enrollment target of 140 patients per arm</li> </ul>	
<ul style="list-style-type: none"> <li>• Patient randomization was stratified by sex, type of disease (cutaneous or nodal disease vs. visceral disease) and age</li> </ul>	

ceiving the combined DTIC plus Allovectin-7® were achieved.

After about 70 patients had completed the study and responses had been evaluated, the committee was to decide whether to allow the study to continue accrual. The criteria to be utilized were prespecified and included safety, overall response rate, duration of response, and disease progression. The committee was provid-

ed interim data, tabulated and summarized in a blinded fashion by the data management contract research organization (CRO) retained by the sponsor. The committee reviewed the interim study data and reported to Vical that, according to the prespecified criteria, there were no reasons identified in the study data to warrant stopping study accrual, and the trial should continue.

A total of 202 patients were enrolled between May 1998 and April 2002. Patient enrollment was distributed among 48 study sites in the United States, which included 24 teaching hospitals and 24 community treatment centers.

### OBJECTIVES AND ENDPOINTS

Final on-study evaluations occurred 24 weeks after the first infusion of DTIC (day zero). Additional courses of treatment were administered to patients who had stable disease or who responded. The protocol sought to determine the effect of Allovectin-7® either on time to disease progression or on response rate. The objectives of the study were to demonstrate either an improvement in the median time to disease progression or an improvement in the rate of objective clinical responses, as described in the protocol abstract.

### PROTOCOL ASSESSMENT OF ENDPOINTS

The study endpoints required total tumor burden to be measured at baseline and at assessment visits by clinical investigators using two-dimensional quantification of tumors that presented at cutaneous and soft tissue sites. Cutaneous tumors were measured at baseline and at subsequent disease assessment visits by direct application of caliper or ruler, while soft tissue lesions were measured most often by computerized tomographic (CT) imaging, as well as by other imaging methods such as ultrasound.

The CT imaging method for metastatic disease assessment has been well-described and represents state-of-the-art imaging capability, yet it continues to present the potential for imprecise measurement of tumors, and the potential for inaccurate selection of lesions as tumors. Imprecise measurement of lesions may be

caused by motion artifact in the patient, poor contrast between the lesion and surrounding tissue, and volume averaging, particularly with small lesions. The potential for inaccurate selection of tumors results from the inability of CT scans to distinguish benign and malignant masses. Ultrasound also suffers many of the same limitations inherent in CT scanning. Because of these inherent limitations a robust objective method is required to estimate total tumor burden that would minimize observational bias.

#### **ADDRESSING THE CHALLENGE OF EXCLUDING OBSERVATIONAL BIAS FOR VICAL: THE APPROACH TO ANALYSIS OF EFFICACY ENDPOINTS AND FINAL OUTCOMES**

The protocol required that an independent safety and efficacy committee evaluate response rate and duration and disease progression by measuring tumors identified on the prestudy, end-of-study, and follow-up visit imaging scans. In accordance with the clinical protocol, Vical convened a Data Safety Review Board during the study to independently evaluate safety and perform an interim analysis of the efficacy endpoints to determine whether the criteria to continue accrual and the trial had been satisfied.

Rather than have the Data Safety Review Board perform the final analysis of the efficacy endpoints, Vical sought to have the patients' outcomes assessed by an entity that was independent of the sponsor and clinical trial management. Accordingly, the sponsor enlisted a third party to organize an independent Endpoint Assessment and Adjudication Committee.

For the independent analysis of outcomes, the sponsor imposed several operating requirements for this independent committee:

- The Endpoint Assessment and Adjudication Committee's process for assessing and adjudicating patient outcomes needed to be rigorously independent from the sponsor to avoid the introduction or appearance of bias,
- The process for data reduction and presentation to the Endpoint Assessment and Adjudication Committee needed to be embargoed from the sponsor,

- The Endpoint Assessment and Adjudication Committee was to have clearly defined, written procedures for assessing outcomes, minimizing introduction of observer bias and preferably by a process that masks the subject's assignment to a treatment group,
- The Endpoint Assessment and Adjudication Committee was to have clearly defined procedures for adjudicating outcomes without ambiguity when reviewers disagreed, and
- The Endpoint Assessment and Adjudication Committee was to have a quality management system that was independent of the reviewers and independent of the sponsor.

Conformance with these requirements was ensured through establishment of a charter for the Endpoint Assessment and Adjudication Committee, which is available for review at <http://www.vical.com/eaaccharter.pdf>.

Maintaining an embargo of the study data from the sponsor required that the sponsor not have access to the analyzed data at any time prior to determination of a final study outcome. The integrity of the embargo was assured by limiting access to data prospectively by procedure, training, and external data management; and retrospectively by collecting declarations from persons involved with the study management and data handling, documenting the extent of their activities and levels of responsibility. An external consultant was asked to review the embargo procedures, interview employee participants, and to certify the integrity of the data embargo to the sponsor's chief executive officer.

#### **INDEPENDENT DATA MANAGEMENT ORGANIZATION TO PRECLUDE THE SPONSOR'S BIAS IN DATA HANDLING**

To maintain independence and minimize the potential for introduction of sponsor bias, Vical retained the services of a CRO for data management activities throughout the duration of the trial. A data management plan and statistical analysis plan, developed by the CRO and agreed on by the sponsor, were employed throughout the study duration. The data management plan and the statistical analysis plan ensured an effective embargo of the study data from the

sponsor, following a single release of the interim efficacy results early in the study. Subsequently, a data embargo was employed that was central to insulating the sponsor from inadvertently introducing bias in the analysis and to assuring the integrity of the efficacy study results.

According to the data management plan, CRO data management responsibilities included receipt of source-verified case report forms direct from clinical study investigators, database design, data entry, data analysis, query generation for resolution by the sponsor's monitors, and generation of reports in accordance with the statistical analysis plan. Written procedures were developed for the accounting and transfer of study case report forms. Written procedures, documented training, and audits were performed by the sponsor's quality assurance unit, which operated independently from the sponsor's clinical operations unit.

#### SELECTION OF AN INDEPENDENT ENDPOINT ASSESSMENT AND ADJUDICATION COMMITTEE

A rigorous selection process was employed to select an Endpoint Assessment and Adjudication Committee vendor that demonstrated affirmatively each of the attributes in Table 3. Personnel from clinical research and development, information technology, regulatory affairs, and quality assurance contributed to selecting the recommended Endpoint Assessment and Adju-

dication Committee vendor, Bio-Imaging Technologies Incorporated of Newtown, New Jersey.

## RESULTS

The significant business risk inherent in a decision to advance a product candidate to a late phase of clinical development can be reduced when there is real and perceived objectivity in the data underlying the decision to proceed in development. The complexity of outcome assessment and the open label design of our pivotal study required an independent assessment of endpoints to ensure objectivity. This approach could be used at either a planned interim or final study analysis of outcomes, in accordance with the study protocol, and the statistical analysis plan.

A charter for an independent Endpoint Assessment and Adjudication Committee was developed to enable a controlled assessment process that would be completely independent of the sponsor. The charter includes the controlled radiological image assessment program developed by Bio-Imaging Technologies Incorporated, and the controlled assessment and reporting process developed by Vical.

The Endpoint Assessment and Adjudication Committee charter was reviewed rigorously in consultation with the FDA, resulting in a state-of-the-art charter for independent assessment of outcomes. During nine consultations or meetings, the FDA advised certain expectations for the Endpoint Assessment and Adjudication Committee charter in order to agree that the endpoint assessment resulting from its use in the pivotal phase 3 oncology trial would provide a reliable basis for the sponsor to determine the results of the trial. The FDA expectations that were communicated to Vical included that the sponsor must be embargoed from the study data throughout the trial conduct, the independent Endpoint Assessment and Adjudication Committee must be a different entity with different members from the Data Safety Review Board, and Endpoint Assessment and Adjudication Committee reviewers should avoid and disclose any conflicting financial interests. Table 4 presents the essential elements of the Vical End-

TABLE 3

Attributes Used in Selection of an Endpoint Assessment and Adjudication Committee Vendor
<ul style="list-style-type: none"> <li>• Validated digital imaging capability in compliance with Title 21 <i>Code of Federal Regulations</i> Part 11 requirements</li> </ul>
<ul style="list-style-type: none"> <li>• Experience assessing digital clinical study outcomes in oncology trials</li> </ul>
<ul style="list-style-type: none"> <li>• Assessments to FDA contributed to an approved license application</li> </ul>
<ul style="list-style-type: none"> <li>• Business proposal and response to questions were prepared with high quality and were timely</li> </ul>
<ul style="list-style-type: none"> <li>• Recommendations from references were robust and unqualified; business was viable and stable</li> </ul>
<ul style="list-style-type: none"> <li>• Cost and terms were competitive</li> </ul>

point Assessment and Adjudication Committee charter.

## DISCUSSION

The same physicians who are involved in a patient's day-to-day care have traditionally performed the assessment of patient outcome in clinical studies. This creates difficulty when attempting to apply uniform response criteria across all study sites in a clinical trial, and more importantly, can lead to a substantial bias in the clinical study results. As the importance of accurate and bias-free data in clinical research and development is paramount, a sponsor who advances an investigational product from phase 2 to phase 3 on the basis of inaccurate conclusions from audited data does a disservice to the affected patient population and does not serve the best interest of its other stakeholders; the impact of advancing from phase 3 to the license application on such a flaw is similar and magnified significantly.

Much of the bias inherent in physician assessment of patient outcome can be addressed by conducting the clinical trial in a double blinded fashion, but this is not always feasible. In the case of Allovectin-7®, performing a double blinded study would have required that a subset of patients undergo deep tumor injections with placebo. This risk to patients was reduced by conducting the study in an open label fashion that limited the performance of deep tumor injections to only those patients randomized to Allovectin-7®. Likewise, one can attempt to apply uniform response criteria across all clinical sites involved in a clinical study, but the application of uniform response criteria is most easily accomplished when patient assessments are made centrally in a controlled and prospectively defined fashion.

The use of an Endpoint Assessment and Adjudication Committee in industry-sponsored pivotal clinical trials is a relative novelty, but one of great import to stakeholders in the clinical research and development arena. By making use of an Endpoint Assessment and Adjudication Committee, a sponsor can expect adjudicated clinical trial data that better represent the actu-

### Key Points for the Vical Endpoint Assessment and Adjudication Committee Charter

- Clearly defined roles of all groups involved (central reviewers, sponsor, contractors, FDA, etc.)
- Written procedures for dealing with data received from study sites (missing scans, poor quality scans, missing exam data, etc.)
- Quality control and quality assurance procedures for the handling of all data in any form
- Written procedures for ensuring blinded review of data
- Written procedure for any data transfers to or from the central reviewers or contractors
- Content and format for final Endpoint Assessment and Adjudication Committee reports
- Prescribed criteria for selecting and compensating central reviewers
- Written procedures for training central reviewers in the systematic assessment of data
- Validation process for all databases used in data analysis
- Procedures for data and material storage used in patient assessments
- Clear definitions for all possible outcome categories (complete response, partial response, stable disease, etc.)
- Defined procedures for adjudicating between central reviewers who do not agree on a given patient's assessment
- Defined training program for central reviewers
- If applicable, a defined procedure for adjudicating between site physicians' assessment and the assessment made by a central reviewer

TABLE 4

al efficacy of the drug under study, and that are less likely to be questioned by the FDA at the time of a license application. This can be very important to companies interested in making sound decisions about continuing or terminating specific development programs.

A properly conducted Endpoint Assessment and Adjudication Committee (Table 4) both reduces physician bias and allows for a greater degree of control over the criteria used for assessing patient outcome. Such committees are particularly valuable when endpoints are subjective and/or require the application of a complex definition and when the intervention is not delivered in a blinded fashion. Endpoint Assessment and Adjudication Committee assessments

reasonably may be applied at interim or final efficacy endpoint analysis, to help to ensure that the data reviewed by DMCs are as accurate and free of bias as possible (4).

Sponsors wishing to enact an Endpoint Assessment and Adjudication Committee for their clinical study have had only limited written guidance from the FDA. What guidance is available does not directly address the structural elements required in an Endpoint Assessment and Adjudication Committee charter or the situations in which the FDA would expect an Endpoint Assessment and Adjudication Committee to be used. Therefore, the processes for conducting an Endpoint Assessment and Adjudication Committee should be defined prospectively and must be discussed with and approved by the FDA. Sponsors should bear in mind the cost and time required to develop a charter for an Endpoint Assessment and Adjudication Committee in a clinical trial and should also be aware of the cost of implementing and completing an Endpoint Assessment and Adjudication Committee evaluation. Costs can easily exceed six figures in U.S. dollars for the entire process.

#### DEVELOPMENT OF AN ENDPOINT ASSESSMENT AND ADJUDICATION COMMITTEE CHARTER

Vical moved to develop a process to show data from clinical investigators to a panel of experts for assessment and adjudication. The Endpoint Assessment and Adjudication Committee char-

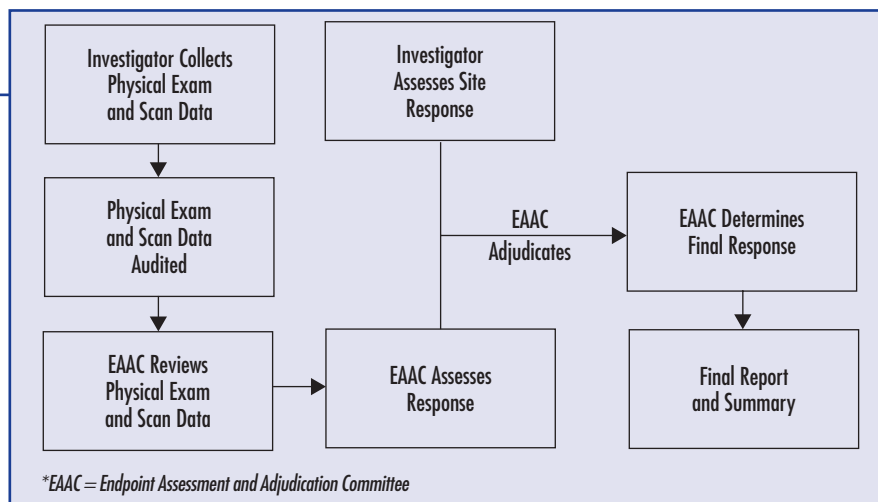
ter was developed de novo through a process that involved selecting the bio-imaging contractor, Bio-Imaging Technologies Incorporated, that designed the CBER's endpoint assessment system. In collaboration with the FDA and Bio-Imaging Technologies Incorporated, Vical developed a state-of-the-art Endpoint Assessment and Adjudication Committee charter, which incorporates Bio-Imaging Technologies Incorporated's digital imaging and assessment technical process. In conjunction with Bio-Imaging Technologies Incorporated, Vical created the assessment questions and designed the committee work process and the quality system. Vical developed a template with content and format for the FDA deliverable final report at <http://www.vical.com/eaaccharter.pdf>. After multiple discussions with the FDA and review by clinical research and development experts, the result was a charter that was acceptable to all parties.

#### CONCLUSIONS

The use of an Endpoint Assessment and Adjudication Committee in clinical trials is likely to reduce bias and can provide robust results that are derived using a set of standard criteria. Such data are likely to result in a greater degree of confidence for decisions made in the course of a drug's development. Perhaps most importantly, for those compounds that are submitted for approval to the FDA, conclusions based on clinical trial endpoint data resulting from adju-

FIGURE 1

Overview of the endpoint assessment and adjudication process.





dication and assessment by an Endpoint Assessment and Adjudication Committee have a reduced risk of the appearance of sponsor or investigator bias, are more likely to be viewed as objective conclusions, and are more likely to reflect the true clinical activity of the compound being evaluated.

We expect that the use of Endpoint Assessment and Adjudication Committees will increase and we feel that the FDA is likely to encourage the use of an Endpoint Assessment and Adjudication Committee in situations where clinical trials are not blinded and where there exists a likelihood of observational bias when determining patient outcomes. Written FDA guidance on the composition and function of Endpoint Assessment and Adjudication Committees is limited for sponsors considering the implementation of an Endpoint Assessment and Adjudication Committees for specific clinical protocols. For this reason, the Endpoint Assessment and Adjudication Committee charter (<http://www.vical.com/eaaccharter.pdf>) may serve as a useful example to other sponsors wishing to incorporate an Endpoint Assessment and Adjudication Committee into their clinical development program.

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Masked Reading assessment and adjudication system, the Nuntio quality control process, and the Response Assessment Evaluation Process, Steve Einstein at Bio-Imaging Technologies, Incorporated. For critically reviewing the Endpoint Assessment and Adjudication Committee charter, Dr. Michael Atkins at Beth Israel Deaconess Medical Center, Dr. Paul Nadler at Nadler Pharma Associates, Dr. George Mills at the FDA Center for Biologics Evaluation and Research, Oncology Branch, and Dr. Tom Fleming at the University of Washington. For critical review of this manuscript, Laura Navalta and Dr. Tom Evans at Vical. All work described in this paper was funded by Vical Incorporated.

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### ERRATUM

The following errors appeared in Ruvuna F: "Unequal Center Sizes, Sample Size, and Power in Multicenter Clinical Trials" in 2004;38(4):387-394.

Fifth Line, 6<sup>th</sup> Line and footnote to Table 1 page 391 change  $\lambda$  to  $\sqrt{\lambda}$ :

$$\sqrt{\lambda} = (Z_{1-\alpha/2} + Z_{1-\beta\lambda}) / (Z_{1-\alpha/2} + Z_{1-\beta})$$

$$Z_{1-\beta\lambda} = \sqrt{\lambda} (Z_{1-\alpha/2} + Z_{1-\beta}) - Z_{1-\alpha/2}$$

Note that the formula is repeated in Table 1 as a footnote and should be changed as well.

Tables 1 and 3 Column Heading:  $1 - \alpha/2$  should be  $1 - \alpha$

All tables use correct results. It is only the text that is incorrect.