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# A Comparison of Community-Based Centers versus University-Based Centers in Clinical Trial Performance

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by

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**A COMPARISON OF COMMUNITY-BASED CENTERS VERSUS UNIVERSITY-BASED CENTERS IN CLINICAL TRIAL PERFORMANCE**

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## ABSTRACT

The success of a clinical trial is largely dependent on the clinical sites that enroll the subjects, complete the follow-up visits, and collect the data. Many clinical trials are conducted using multiple site locations. Choosing such sites to participate in a clinical trial is an important aspect of study implementation. In the past, multi-center clinical trials were conducted mainly using university-based centers. In the last few decades, private practice, or community-based, centers have been included more often in clinical trial research. As more community-based centers participate in clinical trials, it is crucial to examine how these centers might differ from university-based centers.

The purpose of this project was to compare community-based and university-based centers participating in a multi-center randomized trial evaluating treatments for diabetic macular edema. Aspects of recruitment, retention, protocol adherence, data collection, and observance of study required procedures were compared.

Data from 102 participating centers were examined with 40 centers categorized as university-based and 62 centers categorized as community-based. Various measures of trial performance were compared using Wilcoxon rank-sum test, repeated measures logistic regression, and repeated measures analysis of variance (ANOVA), depending on

the variable being compared. Characteristics of the centers and baseline subject characteristics were compared to evaluate for possible confounding.

We found that university-based and community-based centers performed similarly in almost all performance aspects compared. Notable differences included community-based centers becoming certified for participation in the study 90 days sooner on average and university-based centers having half the percentage of ungradable fundus photographs. Overall, it is recommended that community-based centers be included more often in multi-center clinical trials.

# CHAPTER 1. INTRODUCTION

## Background

The success of a clinical trial is largely dependent on clinical centers that enroll the subjects in a reasonable time, complete the follow-up visits within stated windows, and collect the data according to the protocol. Many clinical trials are conducted using multiple center locations. Choosing such centers to participate in a clinical trial is an important aspect of study implementation. In the past, multi-center clinical trials have been conducted mainly at non-profit university-based centers, with clinician-investigators whose research interest and purpose for seeing patients within the university setting was clinical trials. In the last few decades, community-based centers (sometimes called "private practice sites") have been included more often in clinical trials in an effort to increase subject accrual rates, broaden the pool of potential subjects, streamline contractual arrangements with a smaller entity than a university, and centralize institutional review board activities, an option not available for many university-based centers. As more community-based centers become involved in clinical trials, it is crucial to examine how these sites might differ from university-based centers in trial performance.

## Diabetic Retinopathy Clinical Research Network

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative group dedicated to conducting multi-center clinical trials of diabetic retinopathy and its

associated conditions. DRCR.net is funded by the National Institutes of Health (specifically the National Eye Institute), which is a branch of the federal government. The Network was created in order to facilitate evaluation of new treatments for diabetic retinopathy by developing an infrastructure of participating clinical centers organized and prepared to study new treatment approaches as soon as they become available.(Diabetic Retinopathy Clinical Research Network)

From its inception in 2002, the DRCR.net encouraged all clinical centers with access to the necessary equipment to conduct diabetic retinopathy clinical trials to apply for participation. Other requirements for a clinical center to participate in the Network include a qualified investigator, coordinator, photographer, visual acuity technician, and optical coherence tomography (OCT) technician. A qualified investigator has either completed a one year retina fellowship or has completed three years in clinical practice with at least 50% retinal patients. Currently, the DRCR.net consists of 112 active centers and 329 active investigators from 38 states throughout the United States. The open participation concept of the DRCR.net allowed a multi-center network consisting of both university-based and community-based centers to be created, providing a unique opportunity to evaluate how center type affects the conduct of clinical trials.

*Summary of DRCR.net Randomized Trial*

Currently, the DRCR.net has five completed studies, three studies currently in the follow-up phase, and two studies currently recruiting. The data used for the current study are from the second randomized trial initiated by the Network entitled, 'A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema.' The trial is currently in its follow-up phase and the data for this analysis

are current as of February 1, 2008. The purpose of the trial is to compare injections into the eye of triamcinolone acetonide with laser treatment for diabetic macular edema. The study involves required follow-up visits at 4-month intervals with additional visits in between when necessary for care of the subject. The primary outcome visit is at 2 years, and at the time of this analysis, approximately two-thirds of subjects had reached this time point. Data collected at each follow-up visit includes an ocular examination, visual acuity testing, and optical coherence tomography (referred to as OCT) which uses a dim beam of light to measure the thickness of the retina. Special photographs of the retina and lens (referred to as fundus photographs) are also taken annually. The majority of the data is entered at the time of the visit directly on the DRCR.net study website using electronic case report forms. Any edits to the case report forms during the course of the trial are tracked. The data are then monitored by the Coordinating Center for any deviations from protocol. At regular intervals, investigators are required to sign-off on the case report form data that are entered, any edits made, and any protocol deviations the Coordinating Center has identified. Centers are also required to ship the OCT images and fundus photographs to a Fundus Photograph Reading Center (FPRC) within 28 days of obtaining the image or photograph.

**Purpose of Current Study**

The purpose of this study is to compare clinical trial performance of university-based centers and community-based centers participating in a phase III clinical trial being completed by the Diabetic Retinopathy Clinical Research Network entitled, 'A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema.' Aspects of participation, recruitment, retention, and protocol

adherence in the two groups of centers were compared. It is important to note that the majority of centers in this analysis also participated in the Network's inaugural study, which was aimed to evaluate different types of laser treatments. This allowed centers to become familiar with the Network procedures such as electronic case report form entry, measurement of visual acuity with the Electronic Visual Acuity Tester, transmission of photographs and optical coherence tomography images (OCTs) to the Fundus Photograph Reading Center before beginning the phase 3 drug trial. Therefore, the centers being compared in the current study had prior opportunity to adapt to the Network specific study procedures being evaluated.

The purpose of this project was not to determine if one type of center should be included in clinical trials over another. The project was aimed to determine which aspects of trial conduct might be deficient in one type of center so that these deficiencies can be addressed and improved upon in the future. Furthermore, if it is found that community-based centers perform as well or better than university-based centers, the use of these types of centers in government and industry-sponsored large clinical trials may be increased.

# CHAPTER 2. LITERATURE REVIEW

## Oncologic Clinical Trials

There is limited published literature evaluating the conduct of clinical trials at community-based centers compared with university-based centers. The first published evaluations of the clinical trial performance of community-based centers were in multi-center oncology trials. In the late seventies, community hospitals and community-based centers were first being included in large cooperative oncology groups under direction from the National Cancer Institute, which emphasized inclusion of all potential subjects in their studies.(Koretz, Jackson, Torti, & Carter, 1983)

The Eastern Cooperative Oncology Group (ECOG), which consisted only of university hospitals and large treatment centers, began involving community affiliates in 1976.(Begg, Carbone, Elson, & Zelen, 1982) Community affiliates were either smaller hospitals or community-based centers. Since these community affiliates had little or no experience conducting clinical trials previously, their compliance with the protocols and study outcome data were compared with the member institutions to determine whether the objectives of the studies were being met at these new centers. Begg, et al, found that the member institutions had significantly lower ineligibility and protocol-violation rates than the community affiliates. However, the authors believed the difference was not enough to make any practical impact. Inadequate data submission was slightly lower in the community affiliates compared with the member institutions. No difference was found in survival,

response to treatment, or toxicity. Overall, the authors concluded that community hospitals should continue to be included in their clinical trials.(Begg et al., 1982)

A similar analysis by the Northern California Oncology group found that community affiliates performed at least equally to the universities in all but one of the compared aspects.(Koretz et al., 1983) The affiliates had a significantly lower proportion of evaluable subjects based on secondary review of eligibility and treatment. This was mostly due to differences in eligibility determination between the community physician and the central study pathologist, which could be a result of the inexperience of the physicians in determining eligibility. On the other hand, protocol adherence and data completeness rates were higher for the community affiliates compared with the universities.(Koretz et al., 1983)

**Ophthalmic Clinical Trials**

A more recent publication compared community and university-based centers conducting ophthalmic clinical trials.(Bressler et al., 2004) The data were from the Submacular Surgery Trials Research Group, a multi-center research group conducting clinical trials funded by the National Eye Institute. Out of 27 participating centers, 17 were community-based and 10 were university-based. Percentage of total completed exams, completed outcome exams, completed questionnaires as well as time to submit data to the Coordinating Center and images to the Photograph Reading Center were compared. Using only descriptive statistics due to the small number of centers, the authors found that overall community-based centers performed approximately equally to that of university based centers in trial performance with the majority of the centers performing at a high level.

However, the few centers that performed inferiorly to the others tended to be community-based centers. (Bressler et al., 2004)

**Summary**

Due to the limited available data on the subject, especially recently, it is anticipated that this study will contribute greatly to the knowledge of clinical trial implementation at university-based centers and community-based centers. As it is becoming increasingly more common to include community-based centers in large clinical trial networks, it is crucial to determine how the performance of these centers compares with university-based centers.

# CHAPTER 3. METHODS

## Study Design

The current analysis is a retrospective examination of center-specific data collected during a multi-center randomized trial being completed by the Diabetic Retinopathy Clinical Research Network (DRCR.net) evaluating treatments for diabetic macular edema. The data was prospectively collected as part of routine DRCR.net procedures. Outcome measures used to evaluate clinical trial performance were based on real-time electronic data entry of case report forms, edits, protocol deviations, and tracking of image shipments.

### *Eligibility Criteria*

To be included in the analysis, centers had to have been certified in the randomized trial of interest. Of 140 centers that expressed interest in participation, 102 centers were certified. Certain analyses further excluded centers that were certified but never recruited subjects (N = 14) leaving 88 centers remaining.

### *Data Collection*

The trial began with the first center being certified in June 2004 and the first subject randomization in July 2004. A total of 693 subjects were randomized between July 2004 and May 2006. Data collection for these analyses spanned from July 2004 until February 2008. For the baseline subject characteristics, demographic data and a complete medical history was collected from each participant. A glycosylated hemoglobin level and visual acuity

testing results were also recorded. For the site characteristics, data from the 2000 US Census were used to determine region, population and median annual household income for the city in which the center was located.

*Exposure Variable*

The center type was self-reported by each center upon joining the Network and verified by the Coordinating Center. In general, centers with institutional review boards are categorized as university-based, as these centers are research oriented in purpose. These centers also have a university official who completes the contract with the Coordinating Center for performance of the clinical trial. Centers without institutional review boards are generally categorized as community-based, as these centers are private practice oriented in purpose.

*Potential Confounders*

Measures of site characteristics and baseline subject characteristics were compared and evaluated for possible confounding. The two center types were also divided into low and high subject recruitment categories to explore whether number of subjects was a confounding factor affecting clinical trial performance.

*Outcome Variables*

Outcome variables were defined as follows:

- Number of protocol deviations: Count of protocol deviations entered by the Coordinating center per subject.

- Number of case report form edits: Count of changes made to electronic case report forms per subject.
- Number of data queries: Count of electronic queries from the Coordinating Center to the center regarding data issues per subject.
- Number of adverse events: Count of adverse event forms entered per subject.
- Ungradable photographs and OCTs: Whether each photograph and OCT was categorized by the Photograph Reading Center as 'ungradable' or not.
- Number of recruited subjects: Count of subjects enrolled and randomized into the trial at each center.
- Percentage of completed visits: Percentage of follow-up visits required per protocol that were completed; not including visits completed as part of the subject's usual care or visits completed following an injection to assess for safety concerns.
- Percentage of visits in-window: Completed protocol visits were categorized as in-window or out-of-window based on whether they were completed during the protocol-specified time period or "window" for each particular visit.
- Primary outcome visit completion: Active subjects who were past the visit window for the 2-year visit were categorized as having completed or not completed the primary outcome visit. Subjects who were dropped prior to the primary outcome visit were automatically categorized as not completing that visit.
- Primary outcome visit in-window: 2-year visits that were completed were categorized as being completed in-window or out-of-window.

- Dropped subjects: Subjects were categorized as dropped if a final status form was completed by the site to discontinue participation in the study.
- Number of days to become certified: Difference between the date the center expressed interest in the protocol and the date the Coordinating Center certified the center to begin recruiting subjects.
- Number of investigators per center: Count of investigators who completed Network requirements to be certified for participation in the study.
- Number of conference calls attended by the Principal Investigator: Count of monthly investigator conference calls for which the primary investigator is required to attend at least a majority.
- Number of conference calls attended by the Primary Coordinator: Count of monthly coordinator conference calls for which the primary coordinator is required to attend at least a majority.
- Days until sign-off of case report forms: Difference between the date the case report form was entered on the study website and the date the investigator approved the data entry.
- Days until sign-off of edits: Difference between the date the edit was made and the date the investigator approved the edit.
- Days until sign-off of deviations: Difference between the date the deviation was entered by the Coordinating Center and the date the primary investigator approved the deviation.

- Days until submission of photographs and OCTs: Difference between the time the image was taken and the time the item was logged as ‘shipped’ on the study website by the center.

**Statistical Analyses**

Statistical analyses were completed using SAS version 9.1. Summary statistics only are presented for center and baseline subject characteristics, which were evaluated for potential confounding. For outcome variables, the statistical test was chosen based on the type of variable, and all p-values presented are 2-tailed. Normality of distributions was evaluated and non-parametric tests were used where appropriate. Medians and interquartile ranges are reported for all continuous variables to provide information on the distribution of the data. Because of the limitations of multiple comparisons, only p-values $<0.01$ were considered statistically significant.

*Wilcoxon Test*

Continuous variables that contained only one result per center were compared using the nonparametric Wilcoxon test. These included days to become certified, number of investigators per center, number of conference calls attended by the principal investigator and primary coordinator, and number of recruited subjects per center.

*Repeated Measures ANOVA*

Subject-level continuous variables were compared using repeated measures ANOVA to account for potentially correlated data from the same center. This included number of protocol deviations, case report forms, data queries, and adverse events per subject;

percentage of completed protocol visits per subject; percentage of visits completed in-window per subject; days until investigator sign-off of case report forms, protocol deviations, case report form edits; and days until shipment of OCTs and photographs to the Fundus Photography Reading Center.

*Repeated Measures Logistic Regression*

Binary variables with multiple results per center were compared using repeated measures logistic regression with generalized estimating equations (GEE). This included modeling the probability that the visit is completed and if completed, probability that the visit is in-window. The probability that a subject is dropped was also modeled using repeated measures logistic regression. Photograph and OCT quality were compared by modeling the probability that an OCT or photograph was deemed ungradable by the Photograph Reading Center.

# CHAPTER 4. RESULTS

## Center and Subject Characteristics

The study included 102 certified centers. Forty centers were categorized as university-based, and sixty-two centers were categorized as community-based. The participating centers were located in 38 states with 42 centers from Southern states, 25 from Midwestern states, 17 from Pacific states, 15 from Northeastern states, and 3 from Mountain states (Table 1). The largest proportion of university-based centers was from the Midwest (35%) whereas the largest proportion of community-based centers was from the South (52%). According to 2000 U.S. Census data, the population of the cities in which the centers were located ranged from 4,081 to 8,008,278 with the median population in cities of university-based centers being 434,205 and the median population in cities of community-based centers being 135,466 (Table 1). However, the recruitment pool for these centers is not necessarily confined to the city limits so it is not clear whether this difference would affect trial performance. The median annual household income for the cities in which the centers were located was similar between university and community-based centers ($38,459 and $37,426 respectively).

**TABLE 1.** CENTER CHARACTERISTICS ACCORDING TO CENTER TYPE*

| CENTER CHARACTERISTICS | University Based | Community Based |
|---|---|---|
| | N= 40 | N = 62 |
| **Region:** n *(%)* | | |
| Midwest | 14 (35) | 11 (18) |
| Mountain | 1 (3) | 2 (3) |
| Northeast | 6 (15) | 9 (15) |
| Pacific | 9 (23) | 8 (13) |
| South | 10 (25) | 32 (52) |
| **Population:** | | |
| *Median (25th, 75th percentile)* | 434,205 (184,455, 624,064) | 135,466 (42,068, 337,977) |
| *[ range]* | [9,019-8,008,278] | [4,081- 1,953,631] |
| **Population Income:** | | |
| *Median (25th, 75th percentile)* | $38,459 ($31,481, $40,653) | $37,426 ($31,141, $47,498) |
| *[ range]* | [$25,928-$72,057] | [$25,000-$91,162] |

*Percentages do not equal 100 due to rounding

A total of 693 subjects were recruited at 88 of the participating centers with 207 recruited at university-based centers and 486 recruited at community-based centers. Subjects at the two types of centers were similar in age, gender, race, diabetes type, duration of diabetes, baseline HbA1c, and baseline visual acuity (Table 2).

**TABLE 2.** BASELINE SUBJECT CHARACTERISTICS ACCORDING TO CENTER TYPE†*

| SUBJECT CHARACTERISTICS | University Based | Community Based |
|---|---|---|
| | $N_{centers}$ = 35<br>$N_{subjects}$ = 207 | $N_{centers}$ = 53<br>$N_{subjects}$ = 486 |
| **Age** (yrs) | | |
| *Median (25th, 75th percentile)* | 63 (57, 68) | 63 (57, 70) |
| *[ range]* | [38 – 84] | [30-86] |
| **Gender**: Female - n *(%)* | 105 (51) | 232 (48) |
| **Race:** n *(%)* | | |
| White | 139 (67) | 361 (74) |
| Hispanic or Latino | 24 (12) | 64 (13) |
| African-American | 28 (14) | 41 (8) |
| Asian | 9 (4) | 10 (2) |
| American Indian/ Alaskan Native | 2 (<1) | 3 (<1) |
| Native Hawaiian/Other Pacific Islander | 0 (0) | 1 (<1) |
| More than one race | 1 (<1) | 0 (0) |
| Unknown/not reported | 4 (2) | 6 (1) |
| **Diabetes Type:** n *(%)* | | |
| Type 1 | 9 (4) | 20 (4) |
| Type 2 | 188 (91) | 422 (87) |
| Uncertain | 10 (5) | 44 (9) |
| **Duration of Diabetes (years):** | | |
| *Median (25th, 75th percentile)* | 16 (11, 23) | 15 (10, 22) |
| *[ range]* | [0.7-56] | [<.1-59] |
| **HbA1c**[a]**:** | | |
| *Median (25th, 75th percentile)* | 7.7 (6.7,8.7) | 7.5 (6.7, 8.6) |
| *[ range]* | [5.1-14.4] | [4.1-16.3] |
| **Study Eye Visual Acuity- Right Eye: (N=414)** | | |
| *Median (25th, 75th percentile)* | 61 (50, 67) | 59 (50, 66) |
| *[ range]* | [27-73] | [24-73] |
| **Study Eye Visual Acuity- Left Eye: (N=426)** | | |
| *Median (25th, 75th percentile)* | 63 (54, 68) | 62 (55, 67) |
| *[ range]* | [24-73] | [25-73] |

† - only includes sites with randomized subjects (N=88)
* Percentages do not equal 100 due to rounding
a- 50 subjects are missing a baseline HbA1c

## Outcome Measures

Variables related to recruitment and retention were compared according to center type (Table 3). Community-based centers recruited more subjects on average than university-based centers ($p = 0.05$), but the difference did not meet the $p < 0.01$ level for statistical significance. There was no significant difference in percentage of completed protocol visits per center or percentage of visits completed in-window per center. There was also no significant difference in probability that a subject completes the primary outcome visit, that the primary outcome visit is in window, or that the subject is dropped according to center type.

**TABLE 3.** STUDY RECRUITMENT AND RETENTION ACCORDING TO CENTER TYPE

| VARIABLE | University Based | Community Based | P-Value |
|---|---|---|---|
| | $N_{centers} = 40$<br>$N_{subjects} = 207$ | $N_{centers} = 62$<br>$N_{subjects} = 486$ | |
| **Recruited Subjects per Center:** | | | |
| *Median (25th, 75th percentile)* | 4 (2, 9) | 7 (3, 10) | 0.05[a] |
| *[ range]* | [0-18] | [0-31] | |
| **Completed Protocol Visits per Center (%)†:** | | | |
| *Median (25th, 75th percentile)* | 95 (89, 99) | 95 (93, 100) | 0.17[b] |
| *[ range]* | [50-100] | [78-100] | |
| **Protocol Visits Completed in Window per Center (%)†*:** | | | |
| *Median (25th, 75th percentile)* | 86 (76, 93) | 88 (82, 94) | 0.38[b] |
| *[ range]* | [50-100] | [66-100] | |
| **Completed 1˚ Outcome Visits†**:** n (%) | 127/165 (77) | 290/387 (75) | 0.57[c] |
| **1˚ Outcome Visits Completed in Window†*:** n (%) | 121/127 (95) | 285/290 (98) | 0.08[c] |
| **Dropped Subjects†:** n (%) | 30/207 (14) | 90/486 (19) | 0.40[c] |

† - only includes sites with randomized subjects (N=88)
*- of protocol visits that were completed
**- includes subjects who dropped prior to the primary outcome visit as not completed
a- Wilcoxon rank-sum test
b- repeated measures ANOVA
c- repeated measures logistic regression (GEE)

Comparisons of additional variables related to protocol adherence and variables related to data collection are reported in Table 4. There was no significant difference in number of protocol deviations, suggesting that protocol adherence in general is similar at the two types of centers. In terms of data collection, there was no difference in number of adverse events reported per subject, suggesting that reporting guidelines are being followed similarly by the two types of centers. There was also no significant difference in number of case report form edits, data queries from the Coordinating Center, or ungradable OCT images. However, there was a significant difference in number of ungradable photographs (p = 0.002) with community-based centers collecting a higher proportion of these poor quality images.

**TABLE 4.** PROTOCOL ADHERENCE AND DATA COLLECTION ACCORDING TO CENTER TYPE[†]

| **VARIABLE** | **University Based** | **Community Based** | **P-Value** |
|---|---|---|---|
| | $N_{centers}$ = 35<br>$N_{subjects}$ = 207 | $N_{centers}$ = 53<br>$N_{subjects}$ = 486 | |
| | *Median (25th, 75th percentile)* | *Median (25th, 75th percentile)* | |
| *Protocol Adherence* | | | |
| **Protocol Deviations per Subject** | 3 (1, 5)* | 2 (1, 4)* | 0.79[a] |
| *Data Collection* | | | |
| **Case Report Form (CRF) Edits per Subject** | 23 (13, 40) | 26 (14, 45) | 0.79[a] |
| **Data Queries per Subject** | 7 (5, 12) | 8 (5, 13) | 0.44[a] |
| **Adverse Events per Subject** | 8 (4, 13) | 7 (4, 12) | 0.81[a] |
| | *N (%)* | *N (%)* | |
| **Ungradable Photographs** | 45 (3) | 197 (6) | 0.002[b] |
| **Ungradable OCTs** | 22 (1) | 46 (1) | 0.8 [b] |

[†] All variables in table only include sites with randomized subjects (N = 88)
* 31 subjects at university-based centers and 62 subjects at community-based centers had 0 deviations
a- repeated measures ANOVA
b- repeated measures logistic regression (GEE)

Variables related to center and personnel performance in completing Network procedural requirements were examined to determine if there were differences by type of center (Table 5). The time to become certified at community-based centers was significantly lower than the time to become certified at university-based centers ($p < 0.0001$). The days until investigator sign-off of case report forms was significantly higher for community-based centers compared with university-based centers ($p = 0.001$). This difference remained significant when centers were divided into low and high recruiters and center type was compared within recruitment group. There was also a difference in days until sign-off of protocol deviations ( $p =0.02$) and submission of OCTs ($p=0.02$), however these did not meet the $p <0.01$ criterion used for statistical significance. There was no significant difference in number of investigators who completed certification requirements per center, number of conference calls attended per primary investigator, number of conference calls attended per primary coordinator by center type, days until investigator sign-off of edits, or days until submission of photographs (Table 5).

**TABLE 5.** CENTER AND PERSONNEL PERFORMANCE ACCORDING TO CENTER TYPE

| VARIABLE | University Based | Community Based | P-Value |
|---|---|---|---|
| | N= 40 | N = 62 | |
| **Days to Become Certified:** | | | |
| *Median (25th, 75th percentile)* | 208 (128, 247) | 117 (77, 171) | <.0001[a] |
| *[ range]* | [36-574] | [16-326] | |
| **Certified Investigators per Center:** | | | |
| *Median (25th, 75th percentile)* | 2 (2, 3) | 3 (2,3) | 0.59[a] |
| *[ range]* | [1-7] | [1-11] | |
| **Conference Calls Attended per Primary Investigator:** | | | |
| *Median (25th, 75th percentile)* | 7 (0, 15) | 8 (2, 11) | 0.77[a] |
| *[ range]* | [0-27] | [0-22] | |
| **Conference Calls Attended per Primary Coordinator:** | | | |
| *Median (25th, 75th percentile)* | 7 (1, 18) | 7 (2, 15) | 0.76[a] |
| *[ range]* | [0-33] | [0-28] | |
| **Days until Investigator Sign-Off†** | | | |
| *Of Case Report Forms* | 5 (0, 14) | 7 (1, 19) | 0.001[b] |
| *Of Protocol Deviations* | 17 (7, 27) | 19 (7, 40) | 0.02[b] |
| *Of CRF Edits* | 13 (4, 23) | 12 (5, 27) | 0.11[b] |
| **Days until Submission of OCTs†** | 18 (8, 29) | 12 (6, 26) | 0.02[b] |
| **Days until Submission of Photographs†** | 18 (11, 29) | 12 (6, 25) | 0.13[b] |

† - only includes sites with randomized subjects (N=88)
a- Wilcoxon rank-sum test
b- repeated measures ANOVA

# CHAPTER 5. DISCUSSION

## Summary of Findings

In general, university and community-based centers were similar in clinical trial performance. One outcome measure that showed a statistically significant difference for which community-based centers were superior was the number of days to become certified. Outcome measures that showed a statistically significant difference for which university-based centers were superior included days until sign-off of forms and number of ungradable photographs. Although the difference in days until sign-off of deviations was statistically significant, it is not believed that a difference of 2 days is practically important in terms of clinical trial performance.

### *Confounding*

Summary statistics for center and subject characteristics were evaluated for signs of possible confounding. All subject characteristics were similar for the two center types. The two center types varied by site region and population of the city in which the center is located. However, outcome measures did not appear to differ by site region (data not shown). City population was not evaluated further for confounding since it was unclear how wide the recruitment pool for centers spread beyond city limits. It is likely that centers in smaller cities see patients from nearby cities as well. Outcome measures also did not differ by low and high recruitment. There are other possible confounders for which data were not

available for evaluation in this study. These include but are not limited to experience of the investigators and coordinators in previous clinical trials, monetary resources, or other unknown factors.

*Bias*

Whenever the exposure variable is self-reported, as in this case, there is potential for misclassification bias. However, the Coordinating Center reviewed the classification of center type and it is unlikely that misclassification occurred. One factor to note is that centers were self-selected for participation in the trial. These centers were interested in conducting research and were confident that they could adhere to the necessary trial policies and procedures. If instead, community-based centers were chosen at random by the sponsor to participate, the trial performance of these centers may have been different.

*Chance*

Because of the large number of outcome variables being examined, multiple comparisons in this study could have led to false positives. This is likely for variables that were borderline significant including number of subjects recruited, days until sign-off of protocol deviations, and days until submission of photographs ($p = 0.05$, 0.02, and 0.02 respectively).

*Statistical vs. Practical Significance*

Despite the limitations of multiple comparisons, it is believed that the differences in a few variables are valid including days to become certified ($p < 0.001$), days until sign-off of case report forms, ($p = 0.001$), and number of ungradable photographs ($p = 0.002$). Even though these all meet the criterion for statistical significance, it is noted that only the

difference in days to become certified and number of ungradable photographs have practical significance for the success of the clinical trial. An average difference of two days in sign-off of case report forms would not likely affect timely dissemination of the trial results.

*External Validity*

The results from the current study could likely be applied to other multi-center networks in which the same centers participate in several studies, particularly other multi-center ophthalmology research groups. In this study, the centers had experience with the DRCR.net's procedures prior to beginning enrollment in the trial used in the analysis. The results also may be less generalizable to a single study where multiple centers are recruited to participate, as it is not clear if the two types of centers would have the same learning curve for study-specific procedures. It is not clear whether the same conclusions would be found in studies of other diseases. However, the same issues of trial performance affect studies of all disease types.

**Comparison to Other Studies**

The most comparable study performed by Bressler, et al, also found that university-based and community-based centers performed similarly when completing an ophthalmic surgery clinical trial. The study included a smaller number of centers and therefore only presented summary statistics. The current study further confirms that the two types of centers are approximately equal in most aspects of clinical trial performance.

## Conclusion

Since community-based centers performed as well or better than university-based centers in almost all measures of clinical trial performance, it is recommended that these types of centers be considered more often for participation in clinical trial research. The two aspects for which one type was deficient compared with the other should be addressed for future studies. For instance, university-based centers typically take more time to become certified because of obstacles with obtaining approval from the institutional review board and negotiating detailed contracts between the university official and the sponsor for completion of the trial. Community-based centers, on the other hand, are able to use the central IRB, which typically has a quicker turn around time, and have less difficulty promptly setting up contracts with a sponsor for completing trials. The lengthy process for obtaining IRB approval and negotiating contracts at university-based centers needs to be addressed if these centers want to stay involved in multi-center trial research. For community-based centers, the fact that photograph quality was poorer than university-based centers suggests that further training in certain data collection methods may be needed for these types of centers, particularly if research experience is limited.

### *Public Health Implications*

Allowing community-based centers to participate more often in clinical trials will impact those patients who may not have had access to newer, experimental therapies previously or would have had to change doctors to access such therapies. This will also broaden the pool of study subjects in clinical trials, making study results more generalizable. Since the time to become certified in the study was significantly lower for community-based

centers than university-based centers, involving these centers may also be particularly useful when studies need to be completed in a short time frame so that results can be disseminated in a timely manner.

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