The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): Clinical Center Recruitment Experience

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ABSTRACT: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a randomized clinical outcome trial of antihypertensive and lipid-lowering therapy in a diverse population (including substantial numbers of women and minorities) of 42,419 high-risk hypertensives aged ≥ 55 years with a planned mean follow-up of 6 years. In this paper, we describe our experience in the identification, recruitment, and selection of clinical centers for this large simple trial capable of meeting the recruitment goals outlined for ALLHAT, and we highlight factors associated with clinical center performance. Over 135,000 recruitment brochures were mailed to physicians.

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Requests for information and application packets were received from 9351 (6.8%) interested investigators. A total of 1053 completed applications were received and 909 sites (86%) were eventually approved to join the trial. Of the approved sites, 278 either later declined participation or were never activated, and 8 were closed within a year for lack of enrollment. The final 623 randomizing centers exceeded the trial’s recruitment goal to enroll at least 40,000 participants into the trial, although the recruitment period was extended 1.5 years longer than planned. Fewer than a quarter of the sites (22.6%) were recruited from academic medical centers or Department of Veterans Affairs Medical Centers. More than half of the sites (54.7%) were private solo or group practices, which contributed 53% of randomized participants. Community health centers comprised about 8% of the ALLHAT sites and 2.9% were part of health maintenance organizations. More than 22% of the principal investigators reported that they had no previous clinical research experience. In summary, ALLHAT was successful in recruiting a diverse group of clinical centers to achieve its patient recruitment goals.

KEY WORDS: Clinical trial, site recruitment, antihypertensive drug treatment, lipid-lowering drug treatment

INTRODUCTION

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is the largest long-term antihypertensive and lipid-lowering drug intervention trial ever conducted. It is a two-component randomized clinical outcome trial. The first component is a double-blind comparative trial of four antihypertensive drug regimens in high-risk hypertensive men and women aged 55 years and older. The second component, a subset of the first, is a randomized open-label trial of usual care versus lipid-lowering therapy with the 3-hydroxymethyl-glutaryl coenzyme reductase inhibitor, pravastatin. The trial’s design has been previously described [2]. We have recruited 42,419 patients, 10,356 of whom have entered the lipid component, and we expect to follow participants for an average of 6 years until March 2002 [3].

To meet the recruitment goals for this massive trial, a practice-based, “large, simple trial” model was selected. One of the primary goals of the trial was to evaluate the treatment regimens in a broad-based population of older high-risk hypertensives, including African-Americans (original aim ≥ 55%) and women (goal ~ 50%). In this paper, we describe our experience in the identification, recruitment, selection, and training of clinical centers capable of meeting the recruitment goals outlined for ALLHAT and some of the factors and limitations associated with clinical center recruitment performance.

METHODS

Study Organization

The trial is managed by a steering committee and its subcommittees, the National Heart Lung and Blood Institute (NHLBI) Project Office, a Clinical Trial Center (CTC) located at the University of Texas at Houston, and nine Regional Coordinating Centers (RCCs), in addition to the site investigators. The CTC was responsible for site identification, evaluation, approval, and start-up (in addition to its data management, monitoring, and analysis responsibilities). The RCCs assisted the CTC in the coordination of the trial’s recruitment, site
training and monitoring, and data collection functions. The number of sites coordinated by each RCC ranged from 30–102. The full-time equivalents per RCC varied from 0.1–0.4 physicians and 1.2–2.8 nurses during the height of recruitment. The role of the RCCs evolved with time as described below. Since approximately 15–20% of patients were expected to be recruited by the Department of Veterans Affairs (VA), the Memphis VA site was chosen as one of the nine RCCs to provide the administrative coordination of the VA clinical centers. A Canadian RCC at the University of Ottawa was selected to assist in the administration of the Canadian sites. The CTC coordinated the remaining U.S. and Caribbean sites assisted by the remaining seven RCCs.

Site Selection Strategy

As originally envisioned, the majority of clinical centers were intended to come from large primary care private practices and community health centers. The rest were to come from academic medical centers and VA medical centers. It was anticipated that approximately 270 clinical centers would be needed, each randomizing an average of 150 patients over 2 years. The typical ALLHAT clinical center was envisioned to be a primary care group practice with about four to five physicians. This estimate was based upon patient load and diagnostic categories data from the National Ambulatory Medical Care Survey and the British Medical Research Council Mild Hypertension Trial, a primary care practice-based trial [4,5]. Estimates of the proportion of hypertensive patients that would meet ALLHAT entry/exclusion criteria from each practice were calculated using data from the Hypertension Detection and Follow-up Program, the Framingham Heart Study, the VA Hypertension Screening and Treatment Program (HSTP), and the Systolic Hypertension in the Elderly Program [6–9].

Site Identification and Recruitment

ALLHAT clinical center recruitment under the large simple trial model differed substantially from the traditional clinical trial model. The Hypertension Detection and Follow-up Program [10, 11], the Multiple Risk Factor Intervention Trial [12, 13], and the Systolic Hypertension in the Elderly Program [6, 8], three examples of large landmark clinical trials sponsored by the NHLBI, were all conducted under a standard model in which the institute engaged both the clinical centers and the data coordinating centers through separate Requests for Proposals. Both clinical centers and data coordinating centers were typically located at academic medical centers. In contrast, with ALLHAT, the NHLBI published a single Request for Proposals for the selection of the CTC. The scope of work defined in this “master contract” charged the CTC with identifying and coordinating the clinical trial sites in collaboration with the RCCs and the ALLHAT Project Office at the NHLBI.

The initiation of ALLHAT was coincident with rapidly evolving health-care delivery in the United States. Managed care organizations were becoming more common. Therefore, ALLHAT sought to include as many managed care clinics as possible. The ALLHAT Project Office made focused attempts, in collaboration with the CTC, to identify managed care organizations, community
health centers, minority investigators, and military clinics. Because ALLHAT is sponsored by the NHLBI in collaboration with three pharmaceutical companies (Pfizer, Bristol-Myers Squibb, and Zeneca), some representatives and clinical trial monitors in these companies helped with developing mailing lists of their various contacts as potential investigator sites.

Site recruitment was conducted in two phases. During a 6-month internal pilot (Vanguard) phase, 19 sites were recruited for the purpose of evaluating study procedures, site performance, and the ability to recruit a high proportion of Black participants. Sites selected for the pilot were similar to what was anticipated to be the profile of sites to be included in the full-scale phase. They consisted of five VA sites, six community health centers, four academic medical centers, two health maintenance organizations, one private practice site, and one practice self-described as “other practice type.” All vanguard phase clinical centers were located in the continental United States.

For the full-scale phase, it was anticipated that, except for the VA sites for which a finite list could be generated, most U.S. sites would be recruited from a mass mailing campaign or from promotions at major professional meetings. Recruitment brochures were mailed by the CTC to physicians on several mailing lists including the American Academy of Family Practice, American College of Physicians, Society for General Internal Medicine, the Inter-American College of Physicians and Surgeons, and the Clinical Directors Network. Presentations were made at the annual meetings of the American Society for Hypertension, the Canadian Hypertension Society, the International Society for Hypertension in Blacks, the National Association for Community Health Centers, and the National Medical Association. VA investigators were solicited by letters to all 172 VA medical centers, as well as through direct contacts with investigators from prior VA cooperative studies and the directors of VA HSTP clinics. HSTP clinics were established by the VA in the 1970s for specialized screening and management of large numbers of hypertensive veterans. The Canadian RCC was charged with identifying the Canadian sites as part of its contract. Site recruitment brochures mentioned ALLHAT’s goal to enroll 55% Black participants. Not every clinic had to meet the goal, but during the early months of site recruitment, clinics were selected with this aim in mind.

In addition, most of the RCCs began a variety of their own site-recruiting tactics to assist in identifying other investigators. Some RCCs used their personal contacts and knowledge of the providers in their specific communities to identify potential investigators for ALLHAT. Others spoke at local and regional medical conferences. Still others contacted clinics using various insurance lists. Referrals from sites that had proven their ability to perform successfully in ALLHAT was another tactic used by RCCs. This method was particularly effective in the recruitment of the 33 Puerto Rican sites, where one of the authors worked with the RCC to contact other potential investigators, a large insurance provider on the island, and local media.

The clinical center recruitment strategy and coordination differed for VA sites. From the VA’s history of participation in clinical trials, it was anticipated that those sites would have more research experience, a more favorable organizational structure, and a more receptive patient population. Thus, a major focus of the initial VA site selection was to choose centers that could meet the desired goal for African-Americans. The Perry Point (MD) VA Cooperative
Studies Program Coordinating Center assisted in identifying VA sites with the largest outpatient population and proportion of Black patients using analyses from the national VA patient treatment database. Although some VA sites were predicted to have a low proportion of Black patients, it was expected that other VA sites would contribute a proportionately higher representation so that the overall African-American recruitment goal could be met by the VA system as a whole.

Site Evaluation

Several important lessons were learned in the vanguard phase of ALLHAT. Initially, the RCCs were not involved until late in the process of approving sites to be clinical centers. Physicians and clinics submitted an application directly to the CTC (or VA RCC for VA sites), and site approval was granted based on review of this application by the CTC and the Project Office (see the Appendix). The RCCs only began working with the sites following this approval.

After the vanguard phase, when a significant number of the non-VA sites in the United States either dropped out, failed to enroll patients, or failed to obtain regulatory approval until many months after initial approval by the CTC, the decision was made to involve the non-VA RCCs earlier in the initial site selection process. The VA RCC was already involved in the selection of VA sites. The main objectives of earlier RCC involvement in the site evaluation and selection process were to: (1) ensure that each site selected would have a clear understanding of what was required of them in the trial, (2) increase the likelihood that the sites would obtain regulatory approval and begin enrolling patients in a timely fashion, and (3) select sites that would be able to meet their recruitment goal. Earlier involvement of the RCCs also allowed them to collect more detailed data on the prospective sites and establish a working relationship as soon as possible after sites applied for participation in the study. The RCCs assisted in the collection of data on site capabilities and weaknesses while they followed the sites through the IRB approval process.

Screening of potential sites was done by the RCCs by telephone interview with the principal investigator. Having the appropriate patient population and availability of adequate staffing including a study coordinator were considered the most important criteria for determining site approval. The interest, enthusiasm, and experience of the principal investigator were also deemed important. Previous research experience was considered an advantage, but was not a requirement. The RCCs provided explicit information to the principal investigators about the needs and expectations of the trial. All sites were required to submit a recruitment plan early in the approval process, which the RCCs reviewed and often assisted in developing. The recruitment plan was completed before the prestudy training session and was utilized by the RCCs to evaluate the capability of each site, identify potential problem areas, and anticipate needed intervention(s). Finally, an early visit by one or more representatives from the RCC was completed for most sites, both to evaluate the clinic and to provide guidance on integrating the study into the established routine. Site visits were prioritized on the basis of previous clinical trial experience and impressions from the telephone interviews.
Site Reimbursement

Initially, site reimbursement for recruitment included $250 per patient randomized into the hypertension trial, $25 for each follow-up visit, and an additional $25 for each participant randomized into the lipid trial. The clinic received payment for each correctly completed form documenting the visit. This reimbursement schedule was intended only to cover the effort devoted to identifying and consenting patients, as well as time spent completing forms. In accordance with the large simple trial model, data collection was reduced to the completion of only a four-page form for randomization, a three-page follow-up visit form, and a two-page event reporting form. Site reimbursement was not meant to pay for the routine medical care that was part of ALLHAT, which was expected to be covered by insurers.

RESULTS

Site recruitment began in February 1994, and all but a few sites had been recruited by March 1997 (Table 1). The original goal to recruit 270 sites was accomplished by the end of October 1994. However, when only 1218 of a projected 5000 participants had been recruited by the end of September 1994, the site recruitment goal was increased to 400 sites. This new site recruitment goal was achieved by February 1996. However, patient recruitment was not on target, so site enrollment continued. Thirty-three of the U.S. sites were recruited in Puerto Rico, and 30 sites were recruited in Canada. All of the Canadian clinics were activated during the last year of site recruitment.

Over 135,000 recruitment brochures were mailed to physicians and 9351 (6.8%) requests for information packets and application forms were received from interested investigators (Table 1). A total of 1053 applications were re-

Table 1  Cumulative Summary of ALLHAT Site Recruitment Efforts

<table>
<thead>
<tr>
<th>Through Date</th>
<th>Brochures Mailed</th>
<th>Packets Mailed</th>
<th>Applications Submitted</th>
<th>Sites Approved</th>
<th>Sites Rejected</th>
<th>Approved Sites Later Declined/Closed or Inactive</th>
<th>Active Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/94</td>
<td>8,091</td>
<td>717</td>
<td>188</td>
<td>57</td>
<td>22</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>6/94</td>
<td>75,493</td>
<td>2,218</td>
<td>286</td>
<td>133</td>
<td>39</td>
<td>9</td>
<td>124</td>
</tr>
<tr>
<td>9/94</td>
<td>81,961</td>
<td>3,535</td>
<td>508</td>
<td>304</td>
<td>80</td>
<td>8</td>
<td>266</td>
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<td>12/94</td>
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<td>3,641</td>
<td>578</td>
<td>381</td>
<td>102</td>
<td>66</td>
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</tr>
<tr>
<td>3/95</td>
<td>81,961</td>
<td>3,727</td>
<td>613</td>
<td>448</td>
<td>110</td>
<td>105</td>
<td>343</td>
</tr>
<tr>
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<td>3,987</td>
<td>625</td>
<td>480</td>
<td>112</td>
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</tr>
<tr>
<td>9/95</td>
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<td>4,193</td>
<td>641</td>
<td>509</td>
<td>113</td>
<td>142</td>
<td>367</td>
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<tr>
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<td>683</td>
<td>526</td>
<td>113</td>
<td>149</td>
<td>377</td>
</tr>
<tr>
<td>3/96</td>
<td>135,349</td>
<td>8,949</td>
<td>808</td>
<td>651</td>
<td>120</td>
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<td>9,218</td>
<td>890</td>
<td>744</td>
<td>129</td>
<td>180</td>
<td>564</td>
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<tr>
<td>9/96</td>
<td>135,349</td>
<td>9,279</td>
<td>942</td>
<td>789</td>
<td>134</td>
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<td>583</td>
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<td>12/96</td>
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<td>9,330</td>
<td>989</td>
<td>842</td>
<td>136</td>
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<td>1038</td>
<td>880</td>
<td>140</td>
<td>259</td>
<td>621</td>
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<tr>
<td>6/97</td>
<td>135,349</td>
<td>9,351</td>
<td>1049</td>
<td>905</td>
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<td>276</td>
<td>626</td>
</tr>
<tr>
<td>9/97</td>
<td>135,349</td>
<td>9,351</td>
<td>1051</td>
<td>906</td>
<td>144</td>
<td>291</td>
<td>615</td>
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<tr>
<td>12/97</td>
<td>135,349</td>
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<td>1052</td>
<td>907</td>
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<td>295</td>
<td>612</td>
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<td>3/98</td>
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<td>909</td>
<td>144</td>
<td>296</td>
<td>613</td>
</tr>
</tbody>
</table>
ceived and 909 sites (86%) were eventually approved to join the trial. Thus, the overwhelming majority of sites that applied were approved for participation, regardless of clinic type. Of the approved sites, 278 either later declined participation prior to enrolling patients or failed to receive regulatory approval to recruit, and 8 sites with enrolled participants were closed and the participants transferred to other active sites.

The characteristics of the recruited sites are shown in Table 2. A total of 623 sites were recruited in the United States and Canada and contributed participants to the trial, though not all continued participation. Fewer than a quarter of the sites (22.6%) were recruited from academic medical centers or VA medical centers. These sites were responsible for recruiting 26% of ALLHAT participants. More than half of the sites (54.7%) consisted of private solo or group practices, which contributed 53% of randomized participants. While extensive efforts were made at both local and national levels to recruit health maintenance and other managed care organizations into ALLHAT, only 18 agreed to participate, comprising 2.9% of total recruited sites. Community health centers comprised 8% of the ALLHAT sites, and these practices had the highest self-reported concentration of Black participants (72%). The median number of physicians and nurses reported at the non-VA sites were three and two, respectively. More than 22% of principal investigators had no previous research experience. As expected, investigators at university (90.8%) and VA-based (100%) centers more frequently reported having prior research experience.

During the vanguard phase, the median time from site selection to first randomization was 24 days. At the end of the full-scale phase site selection, the median interval was 47 days (Table 3). Previous research experience by the principal investigator (as self-reported) failed to predict either the initial rate of randomization in the first 6 months or the total number of participants recruited. Sites with no previous research experience were able to begin partici-

<table>
<thead>
<tr>
<th>Type of Practice</th>
<th>Number of Sites</th>
<th>Patients Randomized</th>
<th>Sites Reporting &gt;40% African-Americans in Practice</th>
<th>Sites with Previous Research Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private solo</td>
<td>189 30.3</td>
<td>13,791 32.5</td>
<td>94 49.7</td>
<td>146 79.3</td>
</tr>
<tr>
<td>Private group</td>
<td>152 24.4</td>
<td>8,568 20.2</td>
<td>44 29.3</td>
<td>115 75.7</td>
</tr>
<tr>
<td>HMO</td>
<td>18 2.9</td>
<td>1,591 3.8</td>
<td>7 43.8</td>
<td>11 68.8</td>
</tr>
<tr>
<td>CHC</td>
<td>48 7.7</td>
<td>3,641 8.6</td>
<td>34 72.3</td>
<td>18 48.6</td>
</tr>
<tr>
<td>University</td>
<td>71 11.4</td>
<td>3,865 9.1</td>
<td>42 61.8</td>
<td>59 90.8</td>
</tr>
<tr>
<td>VA</td>
<td>70 11.2</td>
<td>7,067 16.7</td>
<td>8 11.6</td>
<td>58 100.0</td>
</tr>
<tr>
<td>Other</td>
<td>75 12.0</td>
<td>3,896 9.2</td>
<td>48 66.7</td>
<td>46 65.7</td>
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<tr>
<td>Total</td>
<td>623 100.0</td>
<td>42,419 100.0</td>
<td>277 45.7</td>
<td>453 77.8</td>
</tr>
</tbody>
</table>

*17 sites have unspecified self-reported % African-American participants, and 41 sites have unspecified previous research experience, and are not included in the denominators for those percentages.

*HMO, health maintenance organization; CHC, community health centers; VA, Veterans Administration medical centers.
Table 3  Recruitment Performance by Type of Site, Principal Investigator Research Experience, % African-American, and Location

<table>
<thead>
<tr>
<th>Type of Site</th>
<th>Number of Sites</th>
<th>Patients per Week per Clinic at 6 Months</th>
<th>Median Days from Approval to First Randomization</th>
<th>Median Number of Randomizations per Site</th>
<th>Median Months to Recruit</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>623</td>
<td>0.8</td>
<td>46.5</td>
<td>38.0</td>
<td>31.0</td>
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<tr>
<td>Private solo</td>
<td>189</td>
<td>1.0</td>
<td>48.0</td>
<td>30.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Private group</td>
<td>152</td>
<td>0.7</td>
<td>39.0</td>
<td>37.0</td>
<td>28.0</td>
</tr>
<tr>
<td>HMO(\text{a})</td>
<td>18</td>
<td>1.0</td>
<td>62.5</td>
<td>42.5</td>
<td>28.5</td>
</tr>
<tr>
<td>CHC(\text{a})</td>
<td>48</td>
<td>0.7</td>
<td>44.0</td>
<td>35.5</td>
<td>22.0</td>
</tr>
<tr>
<td>University</td>
<td>71</td>
<td>0.5</td>
<td>68.0</td>
<td>40.0</td>
<td>36.0</td>
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<tr>
<td>VA(\text{a})</td>
<td>70</td>
<td>0.8</td>
<td>42.5</td>
<td>78.5</td>
<td>38.5</td>
</tr>
<tr>
<td>Other</td>
<td>75</td>
<td>0.5</td>
<td>42.5</td>
<td>37.0</td>
<td>24.5</td>
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<td>Research Experience</td>
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<tr>
<td>Yes</td>
<td>453</td>
<td>0.7</td>
<td>49.0</td>
<td>37.0</td>
<td>34.0</td>
</tr>
<tr>
<td>No</td>
<td>129</td>
<td>1.0</td>
<td>37.0</td>
<td>21.0</td>
<td>39.0</td>
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<tr>
<td>Unspecified</td>
<td>41</td>
<td>0.6</td>
<td>48.0</td>
<td>41.0</td>
<td>52.0</td>
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<tr>
<td>Black Recruitment</td>
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<tr>
<td>&lt;40</td>
<td>413</td>
<td>0.8</td>
<td>46.0</td>
<td>38.0</td>
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<td>≥40</td>
<td>210</td>
<td>0.8</td>
<td>47.0</td>
<td>38.0</td>
<td>34.0</td>
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<td>Location</td>
<td></td>
<td></td>
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<td>Northeast U.S.</td>
<td>106</td>
<td>0.7</td>
<td>55.0</td>
<td>36.5</td>
<td>34.0</td>
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<td>South U.S.</td>
<td>131</td>
<td>0.7</td>
<td>44.0</td>
<td>41.0</td>
<td>34.0</td>
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<tr>
<td>Northwest U.S.</td>
<td>239</td>
<td>0.8</td>
<td>46.0</td>
<td>42.0</td>
<td>35.0</td>
</tr>
<tr>
<td>West U.S.</td>
<td>84</td>
<td>0.6</td>
<td>46.0</td>
<td>37.0</td>
<td>32.5</td>
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<tr>
<td>Canada</td>
<td>30</td>
<td>0.5</td>
<td>63.0</td>
<td>19.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Caribbean</td>
<td>33</td>
<td>2.4</td>
<td>41.0</td>
<td>109.0</td>
<td>22.0</td>
</tr>
</tbody>
</table>

\(\text{a}\)HMO, health maintenance organization; CHC, community health centers; VA, Veterans Administration medical centers.

Pant enrollment in the same or less time than sites whose principal investigator reported previous research experience.

In the first 6 months after site approval, health maintenance organization, private practice, and VA sites had the highest weekly randomization rates of 1.0, 1.0, and 0.8 patients per week, respectively. At the end of randomization, the highest median recruitment was seen at VA sites with 78.5 participants, while median recruitment at private practice clinics and community health centers were the lowest, at 30.0 and 35.5 participants, respectively. The Caribbean sites had the largest median number of randomizations and the shortest interval between site approval and randomization of the first patient (109 participants and 41 days, respectively). Canadian sites had the lowest median recruitment (19 participants) and the longest interval to first randomization (63 days). The Canadian sites were also the last to be recruited and had the shortest period to recruit patients. Clinics that recruited >40% African-Americans were as successful at recruitment as clinics whose recruitment efforts were directed at lower percentages of this demographic subgroup.

The mean number of participants recruited was 68 per site, and the median number was 38 per site. Thus, the median reimbursement received for recruit-
ment was $10,150 per site during the recruitment phase of the trial. Only 72 sites (12%) met or exceeded the original goal of 150 participants per site.

DISCUSSION

The recruitment of the 623 ALLHAT clinical centers from the continental United States, Canada, and the Caribbean was a massive undertaking. Clinical centers, with varying degrees of research experience, motivation, resources, and types of organizational structures had to be identified, evaluated, assisted with regulatory approval, trained, and monitored. Only a minority of the sites were traditional clinical trial research sites. Although 71 centers identified themselves as university-affiliated, the absence of payments for institutional overhead and the limited study reimbursement for investigator and nonphysician staff support likely dissuaded many traditional academic clinical centers from participating. However, the recruitment performance of the sites with limited or no previous research experience was at least as good as that of the more experienced sites.

The first step in achieving the objectives of ALLHAT was to recruit clinical centers that could enroll more than 40,000 high-risk hypertensive participants over age 55 years into the hypertension trial and at least 10,000 of the hypertensive participants into the lipid component of the trial. The trial has been successful in achieving both of these goals [3]. Another strength of the trial is that, with over half of the trial’s centers consisting of private practices, recruitment goals were achieved using clinical centers that more closely resemble the sites providing the majority of care for hypertension and lipid disorders.

Originally, it was estimated that 270 clinical centers would be needed to recruit the required sample size. This was based on the assumption that each center could recruit an average of 150 participants. It quickly became apparent that the estimated number of participants contributed by each center needed to be revised downward, and the number of clinical sites recruited would need to be substantially increased. Only 12% of the ALLHAT centers met the original recruitment goal. One likely reason for the inability of most sites to recruit 150 or more participants was the capitated funding, which was not sufficient (by design) to fund full-time study personnel at an individual site.

Another explanation for the lower than expected per-site enrollment was the unexpected inability to recruit managed care organizations or large group practices. The importance of the study question to the capitated medical environment, and the provision of antihypertensive and lipid-lowering agents in a fixed payment system, should have provided a strong incentive for such sites. Because of the urgency to identify and obtain participation of clinics, a written survey to ascertain the reasons for this lack of interest in a systematic manner was not obtained. However, the perceived loss of productivity because of the study procedures appeared to take priority over any financial incentives or the importance of the trial to the managed care organizations.

In some large group practices, the proposed principal investigator was often unsuccessful in gaining the support of other members of the practice. In fact, some members of large group practices expressed concern about whether the randomized treatments (e.g., those not including a converting enzyme inhibitor in diabetics) conformed to current community standards of treatment.
More intense educational efforts regarding the study objectives and additional resources to hire staff may have attracted more health maintenance or managed care organizations and large practices. However, 24 investigators who responded to recruitment mailings described their sites as health maintenance clinics, and 18 of these are currently participating in ALLHAT. Furthermore, the recruitment objectives of the trial were achieved despite the limited participation of these practice types.

Another important finding of ALLHAT was the demonstration that sites with substantial numbers of Black patients in their practice were able to recruit at the same rate as sites recruiting other populations. For multiple reasons, including the past history of abuses in some widely publicized research studies and lack of investigators with the interest, access, or expertise in recruiting this patient population, the recruitment of Black participants into clinical research trials has been perceived by many to present a formidable challenge [14]. The success of the ALLHAT clinics that did recruit larger percentages of Black participants suggests that given proper motivation, training, and investigators who have developed a trusting relationship with their patients, the recruitment of significant numbers of Black and other minority participants into clinical trials is achievable.

In summary, ALLHAT was successful in recruiting the clinical centers necessary to achieve its patient recruitment goals. It is too early to fully evaluate the performance of the sites with respect to participant adherence and quality of data collection. However, the recruitment goals of the trial have been successfully achieved by these centers.

This study is supported by a contract with the National Heart, Lung, and Blood Institute (NHLBI) federal contract N01-HC-35130. The ALLHAT investigators acknowledge contributions of study medications supplied by Pfizer Inc. (amlodipine and doxazosin), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin), and financial support provided by Pfizer to the NHLBI.

REFERENCES


APPENDIX

Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
Information from Potential Clinical Sites

1. Name and address of practitioner and practice (please print clearly, or attach business card):

<table>
<thead>
<tr>
<th>Practitioners Last Name</th>
<th>Practitioner's First Name</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Name of Practice</td>
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<tr>
<td>Street Address</td>
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<tr>
<td>City, State, Zip Code</td>
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<tr>
<td>Telephone Number</td>
<td>Fax Number</td>
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2. Type of Practice (please circle one):

   a1  Private
   b2  Group
   c3  HMO
   d4  Community health center
   e5  University-based clinic
   f6  Other (specify)

3a. Can your site enroll 150 high-risk hypertensive patients over a two-year recruitment Period? (Please circle one.)
   a1  Yes
   b2  No
   c3  Don't know/Not sure

3b. If you did not answer "yes" to question 3a, what number do you think is feasible?

3c. If you did not answer 'Yes' to question 3a, would you be interested in collaborating with other practices to provide this minimum number? (Please circle one.)
   a1  Yes
   b2  No
   c3  Don't know/Not sure
4. Approximately what proportion of hypertensive patients enrolled at your site are African-American? (Please circle one.)

   a1 95-100%
   b2 80-94%
   c3 60-79%
   d4 40-59%
   e5 20-39%
   f6 0-19%
   g7 Don’t know/Not sure

5. Approximately what proportion of your patients are insured?

   a1 80-100%
   b2 60-79%
   c3 40-59%
   d4 20-39%
   e5 0-19%
   f6 Don’t know/Not sure

6. Approximately how many patients (not visits) does your practice see per year?

   Estimated number of patients per year

7. Approximately what proportion of your patients are hypertensive and aged 60 years and older? (Please circle one.)

   a1 80-100%
   b2 60-79%
   c3 40-59%
   d4 20-39%
   e5 0-19%
   f6 Don’t know/Not sure

8. Approximately what proportion of your hypertensive patients aged 60 and older are also at high risk for coronary heart disease due to one or more of the following: diabetes, left ventricular hypertrophy, diagnosed cardiovascular or peripheral vascular disease or HDL-cholesterol < 35 mg/dl? (Please circle one.)

   a1 80-100%
   b2 60-79%
   c3 40-59%
   d4 20-39%
   e5 0-19%
   f6 Don’t know/Not sure

9. Approximately how many patient-visits does your practice see per week?

   _________ Estimated number of visits per week
10. approximate average frequency with which you see high-risk hypertensives (as defined in Item #8) on stable medical regimens? (Please circle one.)

a1 Monthly or more often  
b2 Every 2 months  
c3 Every 3 months  
d4 Every 4 months  
e5 Every 6 months  
f6 Annually or less often

11. Approximately what proportion of your hypertensive patients have been followed regularly at your facility for 1 year, 2 years, or 5 years?

a______% followed for less than 1 year  
b______% followed for more than 1 and less than 2 year.  
c______% followed for more than 2 and less than 5 years  
d______% followed for more than 5 years

12. What approaches do you currently use to improve patient compliance with medications and appointment-keeping? (Please circle all that apply.)

a1 Reminder postcards  
b2 Reminder phone calls  
c3 Home visits  
d4 Hospital visits  
e5 Other (specify)

13. Would training in specific approaches to improve compliance during the study be an incentive for you to participate? (Please circle one.)

a1 Yes, strong incentive  
b2 Yes, weak incentive  
c3 No feeling either way  
d4 No, weak disincentive  
e5 No, strong disincentive

14. For ascertainment of study endpoints, would you be able to obtain the following documents on your hospitalized or deceased patients at no or minimal additional cost?

<table>
<thead>
<tr>
<th>Document</th>
<th>Yes. In more than 75% of patients</th>
<th>Yes. but in less than 75% of patients</th>
<th>No</th>
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<tbody>
<tr>
<td>a. Hospital facesheet</td>
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<td>b. Hospital discharge summary</td>
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<td>c. Death certificate</td>
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15. Please indicate the numbers of the following staff at your site
   ______ a. Number of doctors
   ______ b. Number of nurses
   ______ c. Number of other medical personnel
   ______ d. Number of other research staff
   ______ e. Number of administrative staff

16. Are computer facilities available at your clinic?
   a1    Yes
   b2    No

17. Please Indicate If you have participated in other research studies (circle all that apply):
   a1    NHLBI studies
   b2    Other NIH studies
   c3    Drug company-sponsored studies

18. Name and address of person who will be primarily responsible for ALLHAT visits and procedures at your clinic - this may be a study nurse or research coordinator.

   Last Name                                    First Name
   
   Street Address
   
   City, State, Zip Code
   
   Telephone Number                                Fax Number

*Please attach CV’s for the persons named in Item #1 and Item #18. Thank you!*