Aside from recruitment, one of the most difficult activities in clinical trials is maintaining a participant’s adherence to the study protocol. Studies show that lost adherence is most commonly related to troublesome life circumstances (65%), with an additional 20% related to adverse effects and 15% related to intercurrent illnesses. By taking the squared function of estimated sample size, trial design allows accommodations for adherence that will be predictably lost. For example, 80% adherence would require an almost 60% increase in sample size, while 50% adherence requires a four-fold increase in sample size. Losses beyond these original assumptions will adversely affect a trial’s original design. In a long-term trial following thousands of participants, the issue of adherence and retention is magnified.

A recent practice-based, randomized, multicenter clinical trial following 42,418 high-risk hypertensive participants responded to this issue by assembling...
existing adherence tools into a single reference resource called the Adherence Survival Kit (ASK). Many of these tools were based on proven adherence concepts, while others were developed in direct response to the distinct and evolving needs of the study clinics.\(^1,3\) The ASK binder was divided into nine sections organized around the four key adherence goals set by the trial leadership (see Table 1). This report presents a detailed account of the development of the ASK, a rationale, and description of the materials included.

**ALLHAT**

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a practice-based, randomized, multicenter clinical trial of pharmacological antihypertensive treatment, and in a subset, cholesterol-lowering treatment. ALLHAT followed 42,418 high-risk hypertensive participants who were 55 years and older and had at least one additional risk factor for coronary heart disease. Participants were randomly assigned to receive one of four pharmacological treatments: chlorthalidone, amlodipine, lisinopril, or doxazosin. Supplemental open label therapy was available for participants who did not meet the treatment goal of blood pressure less than 140 mm Hg systolic and less than 90 mm Hg diastolic on monotherapy. Follow-up visits took place quarterly for one year, and thereafter three times a year for an average of six years.\(^4\) The doxazosin arm of the study was discontinued early in 2000 based upon two factors: the low likelihood of observing a significant difference in the primary outcome by the end of the trial; and a significantly higher incidence of major cardiovascular disease, especially congestive heart failure, in the doxazosin arm compared with the chlorthalidone arm.\(^5\)

ALLHAT participants were enrolled by more than 600 clinics in the United States, Canada, Puerto Rico, and the U.S. Virgin Islands. Of these, 65% were private or group practices, HMOs, or community clinics; 23% were Veterans’ Affairs (VA) or university medical centers; and 12% reported their clinic classification as “other.”\(^6\) Over half of the clinics conducting research for ALLHAT were primary practice clinics.

These clinics experienced many factors that adversely affected their ability to maximize adherence at their clinics. Since ALLHAT did not provide direct support for clinical research staff at any of the clinical sites, staff members with limited research experience were trained to conduct the study at many of the private care facilities. Additionally, recurring employee turnover during the conduct of the trial necessitated repeat training of clinic staff. Further, the evolving health care needs of the aging ALLHAT population required many participants to seek care from non-ALLHAT physicians and specialists who may not have been willing to adhere to the ALLHAT protocol.

While ALLHAT was designed to allow accommodations for predictable losses in adherence, losses beyond the original assumptions of the trial would threaten the success of the study.\(^7\) The recognition of the challenges faced by the ALLHAT clinics, and the long duration of follow-up, resulted in concerns that adherence would become an increasingly greater challenge as the trial progressed.

By January 1998, a decline in overall adherence was notable. For example, approximately 10.5% of participants at 12 months of follow-up had missed two or more of their most recent consecutive study visits. This number increased to 14.6% at 24 months. During the same periods, 15.6% and 19.2% of the participants had stopped blinded study medication. To address this, the NHLBI Project Office and the ALLHAT study leadership adopted four key adherence objectives: 1) keep participants on their study medication; 2) conduct a study visit with each participant three times a year; 3) keep blood pressure controlled below 140 mm Hg systolic and below 90 mm Hg diastolic; and 4) report all study events.

In response to attrition resulting from a long trial duration and other factors, the ALLHAT committee designed tools to fill the need of participant tracking without significantly increasing the study workload of clinic personnel.

While the four key adherence objectives were straightforward, assisting the clinics in achieving these goals proved to be a considerable challenge for the study leadership. During the conduct of the study, many adherence tools were developed to address the needs of the ALLHAT clinics. Many of these tools were based on proven adherence concepts, and others were developed in response to the evolving needs of the clinics. Each of these tools had been distributed to the clinics at different times during the start-up and follow-up phases of the trial, resulting in inconsistencies regarding the availability of these tools across the roughly 600 clinical sites. ALLHAT’s Retention and Adherence Subcommittee assembled the Adherence Survival Kit (ASK) to consolidate all of ALLHAT’s adherence tools into one resource, developed to uniformly distribute these tools to the ALLHAT clinics.

The ASK binder was organized to direct the user to the tools that addressed their most pressing retention and adherence needs. These tools assisted clinics with limited research backgrounds, while providing innovative
ideas to more experienced clinics that were also struggling to maintain the study protocol and reach adherence goals. Further, a distribution strategy was developed to provide the ASK resource to each site and optimize its use among the diverse clinics without a central training session.

Overview of the ASK Program
The introduction section of the ASK presented basic adherence concepts to the clinics in an effort to educate and reinforce the importance of participant adherence and retention as an operational issue in clinical trial management. Inexperienced clinic staff was encouraged to use these tools to develop procedures that would decrease the number of lost participants at their clinics. More experienced clinic staff used these materials to review and reinforce their existing procedures for maintaining contact with participants.

These materials included “Adherence: A Short Course,” from the Handbook of Health Behavior. While this had been used in previous clinical trials, it was adapted to ALLHAT and included in the introduction of the ASK. The course summarized five key points of successful adherence: 1) identifying threatened or reduced adherence; 2) addressing incomplete protocol adherence; 3) maintaining adherence in the majority of participants; 4) using an adherence team approach; and 5) assuring minimum adherence.

The “Red Flags” check list from the same work was provided to help clinic staff identify early warning signs of participants at greatest risk for reduced adherence. The list also highlighted specific behaviors and signals that a participant who is at greatest risk for being lost might demonstrate. Clinic staffs were encouraged to place copies of the checklist in each participant’s chart for use during clinic visits.

The introduction also had a short description of the four key adherence goals of the study, followed by a step-by-step guide on how to use the ALLHAT monitoring reports. These reports were distributed monthly to both clinic and regional staff, and were developed to help manage participant activities and identify possible adherence problems.

Keeping track of your participants
Because of the aging study population, fulfilling the protocol elements was threatened by hospitalization for acute and chronic conditions, as well as the transfer of care because of declining health or changes in health insurance. Movement of participants between states, especially during the winter months, also presented challenges to collecting data within each study visit period. Some study participants developed clinical trial fatigue and lost interest in the study due to its long duration (six years). In response to these factors, the committee needed to find ways to prevent the resulting attrition. Therefore, tools were designed to fill the need of tracking participants without significantly increasing the study workload of clinic personnel.

Materials in this section of the ASK included retention posters developed by ALLHAT staff. These posters were made available to clinical sites to be strategically displayed in the clinic as a continued reminder of the study to the participants. Appointment cards and visit reminder postcards were provided so that participants did not have to commit appointments to memory. These cards also reminded participants to bring their study medication, and specified whether or not the upcoming appointment required fasting for laboratory tests.

To collect contact information that is often not centrally located in the clinic chart, a participant contact information form was designed. This contact information form was completed by the participant and updated yearly. In addition to the form requiring that the participant list his/her own address and telephone number, the form requested the contact information for two additional friends or relatives not residing at the same address as the participant.

Six letter templates were also developed in response to many of the issues faced by study coordinators. The letter templates could be easily copied onto clinic letterhead for immediate use, or an electronic version of the templates could be requested to allow adaptability for the individual needs of a clinic. Some examples of these letters included: a request to participants who had missed two consecutive visits to re-establish...
communication with the ALLHAT clinic; a description for non-ALLHAT physicians explaining the importance of the trial and requesting their cooperation; and a request to participants who had entered a nursing home to maintain contact with the clinic.

A postcard visit was developed for those participants who had an extended absence from their hometown and could not make scheduled in-clinic visits. The postcard could be given or sent to participants, completed by the participant within a set time period, and mailed back to the clinic. Data from the postcards were transferred to the appropriate case report forms for submission. Other tools included a tip sheet on how to transfer a participant to a new ALLHAT clinic and a “Participant Party Kit,” which was an event planner for use in enhancing participant education and social networking among participants.

**Keeping track of study events**

All ALLHAT study events required appropriate medical documentation. Since many participants had multiple sources of care, documentation was often collected from hospitals and medical providers other than those familiar to the ALLHAT clinic. Study coordinators found that letter templates and medical release forms helped reduce the amount of time needed to prepare medical records requests, and increased the likelihood of receiving the

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**Table 1. Table of Contents of the ALLHAT Adherence Survival Kit**

1. **Introduction**  
   - Adherence: A Short Course  
   - Red Flags  
   - ALLHAT Clinical Performance Profile

2. **Keeping Track of Your Participants**  
   - Poster  
   - Participant Contact Sheet  
   - Participant Follow-up Letter  
   - Appointment Card  
   - Visit Reminder Postcard  
   - Missed Visit Postcard  
   - Certified Letter for Two Missed Visits  
   - Nursing Home Letter  
   - Primary Care Provider Letter – MD to MD  
   - Transfer (AL15) Help Sheet  
   - Participant Party Kit  
   - Primary Care Provider Letter – Participant to MD  
   - Letter to a Participant Who is off ALLHAT medications  
   - Letter to a Participant Who Has Had an Event

3. **Keeping Track of Study Events**  
   - Release of Information  
   - NDI Letter  
   - Letter to Family Regarding Death of Participant  
   - Getting a Death Certificate  
   - Medical Records Letter  
   - Vital Check – Provider Phone Numbers  
   - Study Event (AL04) Help Sheet  
   - Medical Records/Death Certificate Help Sheet

4. **Keeping Participants on Study Drugs**  
   - Clinic Visit Script  
   - Telephone Visit Script  
   - Participant Newsletter (Special Edition)  
   - Systematic Rechallenge Letter  
   - Drug Restart Plan  
   - ALLHAT Rechallenge Algorithm  
   - Problem Solving Tips for Working with Outside PCPs  
   - Participant Flyer

5. **Keeping Blood Pressure Controlled**  
   - Algorithm for ALLHAT BP Control  
   - Dosing Pocket Card  
   - Dosing Schedule

6. **Suggestions to Clinics**  
   - Adherence Ideas  
   - Birthday Cards  
   - Anniversary Flyer

7. **Scientific Resources/Frequently Asked Questions**  
   - TOMHS Final Results  
   - TOMHS Table 4  
   - JT Wright, ALLHAT Study: A Trial Long Overdue  
   - ALLHAT Design Paper  
   - LA Grand Rounds  
   - Applegate, Clinical Trials of Elderly Subjects

8. **Finding Your Lost Participants**  
   - Lost to Follow-Up Telephone Script  
   - Lost to Follow-Up Participant Challenges and Solutions  
   - Tips to Remember While Recovering Lost Participants  
   - Lost to Follow-Up Tricks of the Trade  
   - Lost to Follow-Up Resources to Find Volunteers  
   - ALLHAT Job Ideas for Our Volunteers  
   - Nonresponder Letter  
   - Internet Resources to Find Lost Participants  
   - Computer Search Tips  
   - Lost to Follow-up Worksheet

9. **Spanish Materials**  
   - Poster  
   - Participant Contact Sheet  
   - Visit Reminder Postcard  
   - Missed Visit Postcard  
   - Certified letter for Two Missed Visits  
   - Release of Information  
   - Letter to Family Regarding Death of Participant  
   - Participant Newsletter (Special Edition)
requested documents without additional paperwork, requests, or telephone calls.

The collection of death certificates was also difficult for many ALLHAT study coordinators. State laws governing confidentiality made the retrieval of a death certificate difficult in many states. Plus, ALLHAT’s international enrollment meant that the study needed access to death certificates from each of the 48 continental states as well as Puerto Rico, Canada, and the U.S. Virgin Islands. State approval under the National Death Index (NDI) helped to facilitate requests made by the clinic staff on behalf of the study. Letter templates helped study coordinators request these documents from government agencies, hospitals, medical providers, and family members.

In order to facilitate obtaining necessary hospital records, a template for a “Release of Information” was included in this section. This template allowed staff to photocopy the document onto clinic letterhead, have it signed by the participant or his/her next of kin, and then use it in obtaining medical documentation needed by the study. Clinics were instructed to update this release on a yearly basis. In order to expedite requests for hospital records, a letter from the National Heart, Lung, and Blood Institute’s ALLHAT Project Office, which explained that the request was for research purposes, was provided to the sites to be included in their requests for medical records. To assist in collecting hospital records or death certificates for deceased participants, a compassionate and professional letter template was included to gather information and permission from the family.

Because of the specific application and approval process for NDI, letter templates were provided for requesting death certificates from state agencies. These documents specified the ALLHAT NDI approval number that identified the request as part of research and facilitated the retrieval of documents from state agencies. Telephone numbers and fees for all state agencies responsible for handling death certificate requests were also included, along with suggested tips on how to best obtain death certificates. Additionally, “tip sheets” were included to assist study coordinators in identifying study events, completing study event forms, and collecting medical records and death certificates.

Keeping participants on study drugs
As in many large, multicenter trials of long duration, the ALLHAT population encountered many obstacles in maintaining medication adherence for participants. The primary focus of this section was to educate inexperienced staff and increase their comfort level when managing an ALLHAT participant’s medication regimen. This included treatment procedures that could be reviewed quickly, and materials for the participant on the importance of adherence.

This section of the ASK included scripts that were written to give study coordinators step-by-step suggestions on conducting a study visit, including event ascertainment and medication adherence. This section included a drug rechallenge algorithm as well as a restart plan to help staff identify those participants who might be most successful at beginning study medication again. Also included were strategies for working with non-ALLHAT physicians who were assisting ALLHAT participants to keep the subjects on their assigned study medication.

Since participant cooperation is the primary factor in adherence to study medication, ALLHAT published material intended for study participants. An ALLHAT participant newsletter included current study information and was circulated semi-annually. A special edition of this newsletter was developed to help participants remember and understand the purpose and importance of the study, and encourage adherence to their assigned study medication. In addition, a semi-annual participant flyer was initiated to communicate ideas about adherence to the study protocol in lay terms. Examples of the flyer and the special edition newsletter were included in this section of the ASK.

Because coordinators devoted little effort to recovering missing participants, the number of subjects lost to the study grew over time.

Keeping blood pressures controlled
Many of the same issues impacting adherence and retention measures also affected blood pressure. Reinforcement of the blood pressure goal, and use of ALLHAT’s first and second line drugs to effectively manage a participant’s blood pressure, were incorporated into the ASK.

Materials in this section were generated from the protocol and Manual of Operations, and were reformulated to offer an accessible dosing schedule and algorithm reference source to ALLHAT staff members. The dosing schedule was printed on a pocket-size laminated card that included the blood pressure goal, a step-by-step description of how to increase the dose of study medication and/or add supplemental medications to
control blood pressure, and a table identifying the ALLHAT doses and equivalent doses of each medication. The card provided a different manner of viewing the step-by-step increase of medication to reach the blood pressure goal. For convenience and quick reference, the dosing schedule, algorithm, event reporting, and medication tips were also developed on a pocket card.

**Clinic suggestions**
Bonding between study coordinator and participant often occurs during a study, and can be the cornerstone of successful adherence and retention. However, this relationship is often difficult to maintain in the constantly changing nature of today’s medical environment. This section of the ASK included suggestions to enhance the relationship between the clinic staff and the participants.

These were compiled in a list focused on making the study visit more convenient for the participant (i.e., how to reduce the time for each study visit) and on making the participant feel more comfortable. Formats for birthday cards and study participation anniversary flyers also provided opportunities to contact participants outside of a visit and acknowledge important events in their lives, besides their study involvement.

**Scientific resources/frequently asked questions**
Although much of the scientific literature on participant adherence and retention in clinical trials is anecdotal, some data and factually based reports are worthy of note. Copies of published reports were provided to clinical staff so that they could study these in greater detail. The objective was to provide clinical staff with a small but comprehensive collection of articles to help them understand and formulate plans to maintain and improve participant adherence and retention.

Articles provided in this section of the ASK were Follow-up and Adherence in Clinical Trials of Elderly Subjects by Applegate. The final results paper from the Treatment of Mild Hypertension Study provided documentation of the low frequency of adverse effects related to the study medications used in ALLHAT. The ALLHAT study design paper was also included so that clinic staff could reference the intent, focus, and importance of the study. An article from *Urban Cardiology* was included to further explain the importance of ALLHAT and its successful completion, particularly in reference to minority patients. Finally, questions and answers from a featured discussion session during the 1997 ALLHAT Investigators’ meeting were included as a review of relevant protocol issues.

**Finding your lost participants**
Since many study coordinators focused their efforts on maintaining active participants and devoted little effort to recovering lost participants, the number of participants lost to the study grew over time. As planning for closeout began, another section was added to the ASK to help coordinators with the difficult task of finding and maintaining contact with lost participants.

This process included identifying participants who were mislabeled as refusing further study participation, when in fact they were only refusing to take the study medication or refusing to attend clinic visits. Because re-establishing contact with lost and refusing participants was imperative for obtaining closeout information and vital status of the cohort, the kit provided tools to find lost participants and formerly misclassified refusals. The ASK also provided ideas on effective methods of contacting participants, and maintaining the participant’s interest after re-establishing contact.

Internet and computer searches were an important resource for finding lost participants. In order to help educate study coordinators on how to utilize this technology, a Web resource and computer search guide was included in this section of the ASK. A worksheet helped coordinators keep track of the information gathered during these searches. A telephone script summarizing challenges and alternatives aided in obtaining the most information when conducting telephone conversations with participants or their family members. Once a participant was found, it was important to maintain contact. For this focus, “Tips to Remember When Recovering Lost Participants” was included along with a list of ideas to enhance and maintain participant adherence. An additional resource was a letter template designed to capture the attention of nonresponding participants. Finally, a list of local volunteer organizations was included, along with ideas on how to utilize volunteers to help with the study.

**Spanish materials**
Study clinics in Puerto Rico and U.S. regions with large
Spanish-speaking populations needed ASK resource materials in Spanish. This section included samples of all adherence materials that were made available in Spanish, so all study coordinators with Spanish-speaking participants had appropriate materials readily available. Materials provided in Spanish included: retention posters, contact information forms, visit reminder postcards, missed visit postcards, all letter templates, release of information forms, special edition participant newsletters, and the Participant Party Slides.

**Distribution and implementation of the ASK**

Key elements of the ALLHAT adherence strategy were to facilitate the uniform distribution of the ASK and to successfully motivate the clinics into using the adherence tools. Initially, the Retention and Adherence Subcommittee set out to introduce the ASK during face-to-face meetings. These sessions would allow the regional coordinating staff to highlight specific tools offered in the ASK that would be most beneficial in dealing with issues specific to each clinic. The nine Regional Coordinating Teams introduced the kit to some of the clinics during specially organized working lunches, dinner meetings, teleconference calls, or individual site monitoring visits. Distribution to some clinics was accomplished during regional sessions of the April 1999 Investigators’ Meeting, where many aspects of the ASK were featured in both plenary and breakout sessions. Reinforcement of key elements was accomplished during subsequent regional and national investigator meetings.

This distribution strategy resulted in active discussion and problem-solving of medication and blood pressure issues between clinic investigators and ALLHAT leadership, producing a greater understanding of the study goals during the follow-up phase of the trial. Individualized distribution of the ASK was done collaterally with discussion of specific adherence problems encountered during telephone or face-to-face visits, creating an environment for positive interaction between the clinics and the study. The result was more purposeful and constructive interaction between the study leadership and the clinics during a crucial time in the trial.

**Discussion**

Development of the ASK grew out of the need for ALLHAT clinics to maximize participant adherence to the study protocol. Since the focus of many of the ALLHAT clinical centers was primary care, routine adherence activities (appointment reminders, conducting appointments within study visit periods, tracking and finding lost patients) fell outside their normal work scope. This lack of basic adherence understanding, coupled with the research naïve of the clinical centers, led the study leadership to develop the ASK. The ASK was an organized and consistent approach to the execution of the study protocol. This comprehensive approach included overall adherence goals with an emphasis on prevention and specific approaches to participants who exhibited any level of reduced adherence.

In the winter of 1999, a questionnaire was developed and distributed to those clinics who had been provided with an ASK and were still actively involved in ALLHAT (n = 544). With a 78% response rate, the survey revealed that 77% of clinics felt that their adherence issues were addressed by the ASK, and 88% of clinics reported using the tools provided in the ASK. Only 12% reported never using it in their study activities.

While the prevention of adherence problems is recognized as a key issue, adherence and retention have historically been given fullest attention only after recruitment goals have been met. However, it is essential to be attentive to potential adherence issues during recruitment and screening, and to establish an adherence and retention protocol at the onset of a trial. The exclusion of a patient because of potential threats to adherence will better serve the adherence and retention goals of the study and its final power to answer the study question, a case of quality over quantity. Further, an initial focus on prevention of “lost” participants will alleviate the need to find or reinstate these study subjects later.

The experience of having a standardized approach to adherence practices is strongly recommended for other trials, specifically those trials in private practice clinics. The demands of business in private practice settings require an adherence program that is easy and acceptable, since ease of implementation and acceptance by clinical staff is crucial.

**Conclusion**

The Adherence Survival Kit was an organized approach to the management of retention and adherence issues in a large, long-term clinical trial. It was developed primarily for research-naïve clinics, in response to the staff turnover experienced by many of the ALLHAT clinics. The ASK was well received by the ALLHAT clinics and was regarded as an effective tool for use in maintaining study participants on the protocol. Because adherence to study visits and medication is difficult to regain, an adherence protocol should be started early in any trial. An adherence guidebook and ASK-like tools can direct clinics to focus on retention and adherence details during all phases of a large simple trial.

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Christine M. Lusk, MPH, Judy Bettencourt, MPH, and Charles E. Ford, PhD, are with The University of Texas Health Science Center School of Public Health, Houston, TX, (713) 500-9520, fax (713) 500-9530, email: spressel@sph.uth.tmc.edu. Lillian Carroll, RN, MS, and Sheila Sullivan, BA, are with the Albert Einstein College of Medicine Bronx, New York, NY. Debra Egan, MPH, and Chuke Nwachuku, DrPH, are with the National Heart, Lung, and Blood Institute, Bethesda, MD. Connie Kingry, RN, BSN, Janice Johnson, BS, and Jeffrey L. Probstfield, MD are with the University of Washington Medical Center, Seattle.

*To whom all correspondence should be addressed.