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Closeout of the HALT-PKD Trials

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Abstract

Background—The HALT Polycystic Kidney Disease Trials Network consisted of two randomized, double blind, placebo-controlled trials among patients with autosomal dominant polycystic kidney disease. The trials involved 5–8 years of participant follow-up with interventions in blood pressure and antihypertensive therapy. We provide a framework for designing and implementing closeout near the end of a trial while ensuring patient safety and maintaining scientific rigor and study morale.

Methods—We discuss issues and resolutions for determining the last visit, tapering medications, and unblinding of participants to study allocation and results. We also discuss closure of clinical sites and Data Coordinating Center responsibilities to ensure timely release of study results and meeting the requirements of regulatory and funding authorities.

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Results—Just over 90% of full participants had a 6-month study visit prior to their last visit preparing them for trial closeout. Nearly all patients wanted notification of study results (99%) and treatment allocation (99%). All participants were safely tapered off study and open label blood pressure medications. Within 6 months, the trials were closed, primary papers published, and 805 letters distributed to participants with results and allocation. DCC obligations for data repository and clinicaltrials.gov reporting were completed within 12 months of the last study visit.

Conclusions—Closeout of our trials involved years of planning and significant human and financial resources. We provide questions for investigators to consider when planning closeout of their trials with focus on (1) patient safety (2) dissemination of study results and (3) compliance with regulatory and funding responsibilities.

Keywords

Closeout; unblinding; regulatory; data coordination; patient safety

Introduction

The overwhelming recommendation from the field of clinical trials is to plan early for closeout.[1–3] Authors have made recommendations on designing closeouts to ensure patient safety, follow-up, and timely publications for trials reaching their expected end[1–4] while others have described the aspects of shutting down studies earlier than planned. [5–7] Specific recommendations entail having a common closing date[1] and post-treatment follow-up[1, 4], preparing patients psychologically for trial end[1], updating patient contact information[1, 2], getting staff input about operational details and feasibility of closeout plans[3], including plans for early termination[3, 6], ensuring adequate training for data collection and entry[2], allowing for adaptable strategies[2] and flexibility in staff roles[6], keeping communication flowing with sites[2, 6], and allowing time and personnel for closeout[6]. However, when closeout has not been planned early, minimal guidance exists to help investigators prioritize design and conduct issues during the end of a long-term trial.

The HALT Polycystic Kidney Disease Trials Network consisted of two placebo-controlled trials testing blockade of the renin-angiotensin-aldosterone-system (RAAS) on disease progression among patients with autosomal dominant polycystic kidney disease (ADPKD). [8–10] Both trials involved tightly controlled blood pressure (BP) parameters which were targeted using masked study drugs and open label antihypertensive medications. The trials were conducted in the United States from 2006–2014 with 1044 patients followed for 5 to 8 years depending on the date of enrollment (2006–2009). In this paper, we share with trialists the lessons learned from designing a closeout achievable within 2 calendar years of study end for the last enrolled patient. Our goal for closeout was optimizing patient safety while maintaining scientific integrity for fast dissemination of results. We discuss issues around determining the last visit, tapering medications, participant unblinding procedures, site closure, and release of study results.

HALT PKD trials

HALT PKD Study A was a 2×2 factorial trial designed to test if dual therapy of angiotensin converting enzyme-inhibitors (ACE-I) and angiotensin II receptor blocker (ARB) was superior to ACE-I monotherapy and if low BP control (systolic 95–110 and diastolic 60–75 mm Hg) was superior to standard BP control (systolic 120–130 and diastolic 70–80 mmHg) for disease progression (See Figure 1). The primary outcome of Study A was the percent change in total kidney volume (TKV) measured by magnetic resonance imaging (MRI) at baseline, 24 and 48 months. HALT PKD Study B compared ACE-I/ARB combination therapy with ACE-I monotherapy on time to a 50% reduction of baseline estimated glomerular filtration rate (eGFR), end stage renal disease (ESRD) or death in individuals with more advanced kidney disease (eGFR 25–60 mL/min/1.73m²). All Study B hypertensive ADPKD participants were treated to the standard BP control. Both trials were conducted in 7 participating clinical sites (PCCs) with a data coordinating center (DCC), image analysis center (IAC), central laboratories for serum and urine samples, and an independent Data and Safety Monitoring Board (DSMB). Both trials began recruitment in 2006 with the last participant randomized in 2009. Originally, the trials were designed to follow participants every 6 months through 2012 with varying followup of 3–5 years depending on the participant's date of enrollment. In August 2010, the DSMB approved the extension of Study A through mid-2014 which would allow for an additional TKV measurement at 60 months for all participants due to supporting evidence from a long-term observational study that baseline TKV was associated with long term GFR and was highly predictive of progression to stage 3 chronic kidney disease (CKD).[11] All Study A patients were to be followed for at least 5 years (up to 8 years for some). In August 2012, the DSMB approved the extension of Study B until mid-2014 due to lower than expected number of endpoints, therefore, ending at the same time as Study A. Details about the HALT PKD protocol and results have been previously published. [9, 10, 12, 13]

Closeout issues to be resolved

In early 2012, the Data Coordinating Center (DCC) was charged with developing formal plans for the closeout of the trials. Of note, the DCC served as both the data coordinating and clinical coordinating center. In addition, the DCC was moved from the original institution to the University of Pittsburgh in 2009. In 2010–2011, there was turnover in the lead nurse coordinator and the principal investigator positions of the DCC. With all the DCC transitions, operational details regarding closeout had not been addressed as the investigators had focused on recruiting, follow-up, and day to day operations.[3] Using the framework for the Hypertension Detection and Follow-up Program (HDFP),[7] the Closeout Committee was formed with just over 2 years before the end of patient follow up. This major effort was undertaken by two clinical investigators and a coordinator from each site (Participating Clinical Center, PCC) under the direction of the DCC's Principal Investigator, lead statistician and research coordinator. By involving study coordinators, the committee appreciated key operational insights to protocol implementation and participant care. The Committee met monthly to solidify plans for study closeout with the objective being “to ensure a safe, organized, timely closeout at all levels of the HALT-PKD clinical trial that includes the participant, PCC, and DCC.” The aim was to ensure participant safety while

maintaining integrity of the clinical trial. At the participant level, the major protocol issues to be resolved were determining which visit prior to July 2014 would be each participants last study visit, tapering BP medications, transitioning care to the local physician, unblinding participants and notifying them of the study results. At the site level, the major issues were development of milestone checklists to ensure proper closeout of all study activities at the PCC. At the DCC level, the major issues were determining final database lock, developing a timeline for publication of the primary papers, delineating tasks and resources needed for data sharing responsibilities, and defining regulatory compliance milestones and timeline.

Closeout of Participants

Participants' BPs had been medically managed on open label and masked study medications for 5 to 8 years which created complexity in tapering and transitioning their care to their local primary care provider (PCP) or nephrologist.

Timing of the final visit

Per protocol, HALT participants were to be followed at the PCC every 6 months with scheduled 3 month phone calls through mid-2014. When reviewing the literature, we found different strategies for final study visits based on the circumstances of the trial ending. If trials ended prematurely for safety or efficacy reasons then final visits were planned for all participants in a condensed period of time. We did not feel this was appropriate for HALT participants since the trial was on target to end without premature stopping. The question arose "Should the participants go off drug at the 6 months prior to the final 6 month visit?" This approach would truncate the last 6 months of follow up on drug which would not be ideal, particularly if combination therapy was effective. Therefore, the final visit was chosen to be the last expected 6-month visit prior to July 2014 so patients would close out of the study remaining on study drug and open label drugs until that visit. This also allowed planning the workload for the coordinators at the sites rather than have an exceptionally high density of visits. The target window for 6 month visits was $\pm$ 1 month so coordinators were encouraged to schedule participants earlier in the window and no later than June 30, 2014.

Tapering of medication

The next issue pertained to determining the protocol to safely taper participants off masked study drug with open label hypertension medication(s) (Supplemental Table 1). As part of the original protocol, Study B participants had been tapered off masked study drug when they reached a study endpoint of ESRD or 50% reduction in eGFR. The study physician had adjusted the participant's open label BP medications after study drug withdrawal before transitioning care to the subject's private physician. We planned for a similar protocol to be used for all participants in both studies at their final in-person visit (closeout visit) with the expectation of complete tapering of blinded study medication within 4 weeks (Supplemental Material). Participants would be reminded of the need to measure their blood pressure regularly during and after tapering. To ensure the safety of the participants, a 2-week monitoring call and an 8-week post closeout follow-up phone call were added to monitor for adverse symptoms and serious adverse events.[2] This follow-up was mandated by our

industry sponsors since study drug was being provided at the last in-person visit for most patients. Similar post-treatment follow-up was recommended or conducted in other studies but with biochemical and hematological measures obtained.[1] Patients who received medications from the research pharmacies at the final in-person visit were only provided enough to maintain safe BP per protocol within the 8 week time frame for follow up. At the 8 week follow-up call, the participant would have reached the end of their study participation and immediately following the call would be considered completely off protocol. Any remaining drugs from the research pharmacy were to be returned to the PCC.

Penultimate visit[2]

We defined the ‘penultimate visit’ to be the 6-month clinic visit prior to the final in-person visit for each participant (approximately 6-months prior to each participant’s closeout visit). At the penultimate visit, the study team would convey the importance of the last visit and what to expect during that visit.[2] The Closeout Committee felt strongly that clinical sites needed to not only prepare patients for tapering of medications and transition of care but to mentally prepare patients for the end of relationships formed with the study team over the years.[1, 2, 7] A questionnaire was developed with questions about the patients’ contact information, access to primary care physician/nephrologist, expected insurance status, and wishes of being notified about study results and treatment allocation (Table 1).[1, 7, 14] We also planned to encourage patients to schedule appointments with their primary physician or nephrologist within 30 days of their final clinic visit to ensure continued BP medical management.

Unblinding of study participants

No standard practice exists for the “unblinding” of trial participants to their allocation or study results.[15] We agreed with others in the literature that participants should receive their study allocation and individual study results as there was no justification for nondisclosure.[3, 14] There was some concern about protecting the wishes of participants who wished to remain blinded.[15] Treatment allocation could not be provided at the final visits due to the structure of these visits occurring over a 6-month period (January 2014 through June 2014) prior to the release of study results to investigators. We decided disclosure of allocation and results would occur within a month of the primary results being released via medical journal publications. A similar approach of offering unblinding after release of study results was used in larger, double-blind trials [2, 15] in contrast to other studies which have unblinded at the final visit.[1] We did not consider having participants guess their study allocation at their last visit.[16] In discussions about release of participant results, many site investigators felt that by the time of unblinding, staff and resources available to carry this out would be minimal. To minimize investigator burden and decrease the likelihood of human error, the DCC developed a capability for sites to generate letters with study results using the web-based data collection system. A letter for each participant and the participant’s PCP/nephrologist[15] could be generated by the site team populated with the participant ID, treatment allocation, the participant’s last measurements in the study, and the final study results (Figure 2). The letters could then be sent to the participants by certified letter or electronic mail. [14]

Approval of Final Plan for Participant Closeout

Steering Committee approval for closeout procedures at the participant level including a detailed timeline for notification letters (Figure 3) occurred just 6 months prior to the first penultimate visit (Figure 4). Immediately upon approval, the procedures were submitted to all IRBs (see Supplemental Material), programming began for the new data to be collected indicating participants' wishes for unblinding, and projections for masked drug usage were made to ensure proper coverage and decrease costs. A coordinator face-to-face training was held in September 2013 just 3 months prior to commencement of the participants' closeout visits beginning in January 2014.[7]

Results of Participant Closeout

Among full participants (n=671) (those who were not lost to follow-up, had not met an endpoint (Study B) or had not stopped taking study drug), 93% had a penultimate visit (61% of all randomized participants). Within this group, 99% wanted to be notified about the study results, 94% wanted their PCP or nephrologist to be notified about the study results and 99% wanted to know their study assignment. Ninety-six percent of full participants (n=605) had a closeout visit from January 2014 thru June 2014 and were successfully tapered off study medications with no study related serious adverse events. Approximately 41% of participants had reached a study endpoint (Study B) before closeout or were no longer on study drug at the time of their last visit. These participants were notified about the end of the study via mailed letter from the corresponding site investigator. Between December 2014 and March 2015, 805 letters were generated for distribution to HALT-PKD participants and 698 letters were generated for their PCP / nephrologists. Most letters were sent by e-mail (62%) which decreased costs.

Closeout of the Clinical Sites

Closeout of the sites was designed using the International Conference on Harmonization Guideline for Good Clinical Practice. The trial would close at the sites using four milestones: participant care, pharmacy and drug activities, laboratory samples, and imaging (Supplemental Material).[17] The first milestone certified that the last participant had completed his final 6- month in-person visit at the PCC, the source document review for all participants had been completed, all drug tapers had been initiated and/or completed, research managers had been notified that the last participant had been seen, all activities in the clinical research facilities were completed and materials were removed, and all data entry was complete. The second milestone certified that all pharmacy related activities were completed including successful tapers for all participants, destruction of all drug supplies, updating of destruction logs, and removal of all study materials from research pharmacies. The third milestone pertained to all blood, urine, and genetic samples. The site investigator certified that all samples were shipped and resulted per protocol, all excess samples were destroyed, all destruction logs were updated, and all study documents were removed from the research laboratories. The final milestone pertained to magnetic resonance images for Study A participants. The site investigator certified that the last Study A participant's images were de-identified and transferred to the IAC, the final images had resulted, and all study materials were removed from the radiology department. Staff from the Data Coordinating

Center made final monitoring visits (FMV) to all sites[6] in a two month period to ensure all milestones had been reached. They also provided assistance when there was lack of progress in any aspects of the closeout process largely due to staff attrition.

Closeout Activities of the Data Coordinating Center

The DCC closeout activities included data cleaning efforts prior to the closeout of the trial, conducting analyses for the primary papers for timely submission, compiling a master regulatory file for the sponsor, the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), and fulfilling reporting obligations to the NIDDK data repository and clinicaltrials.gov.

Data Cleaning

Data cleaning results for primary and secondary outcomes (including lab values and images) were sent to coordinators at 16, 10, and 2 months prior to the final closeout visits. Another data clean focused on out of range items, missing data, or odd-patterned data from the beginning of the study and was done approximately 9 months and 2 months prior to the last inperson patient visit. We cannot emphasize the importance of the data cleaning occurring many months before the final close as others have highlighted.[2] In fact, with our experience, we would recommend this occur on a regular basis as quality control to ensure not only the high integrity of the data but also to ensure any issues can be resolved while staffing at sites is fully available.[4]

Primary Publications

The target date for release of the primary results was determined by the date of the annual conference for the American Society of Nephrology (November 11–16, 2014). Nearly nine months prior to this meeting, a lead investigator contacted the *New England Journal Medicine* requesting consideration for our manuscripts to be reviewed with quick turnaround prior to the conference such that the papers could be simultaneously presented at the meeting and released online. Upon receiving approval for this request, the study statisticians began developing statistical programming for the primary results papers including standardized tabular output and graphs. Preliminary database lock was September 1, 2014, 2 full months after the last in-person patient visit, and final database lock was on October 1, 2014 (Figure 4), 3 full months after the last visit[2] where no further data or corrections were accepted into the database.[4] Similar to the HDFP study[7], a writing team of the lead authors, senior authors, and the DCC biostatisticians was established in the spring of 2014 and immediately developed the timeline for writing the two primary papers. The introduction and methods were to be drafted by mid-June 2014, 2 weeks prior to the last patient's final visit; unblinded results would be sent to the writing team the day after the last patient's final visit; within 3 weeks, drafts of the manuscripts would go to the rest of the Steering Committee, co-investigators, and NIDDK for review; 2 weeks later a revised draft would go to the masked drug sponsor for approval; and 1 month later a final draft would be sent to the journal. Open communication and coordination with the journal staff was critical.[3] Our trials' results were published online[12, 13] and presented at the national meeting within 4 months of the last in-person patient visit. Our decision to begin statistical

programming months prior to study end, to use a small writing team who received unblinded results for drafting the papers, then disseminate to the entire group of investigators was critical to staying on time with delivery of the papers to the journal.

Master Regulatory File

The Master Regulatory File (MRF) was created by the DCC to contain all regulatory documents needed by NIDDK for FDA reporting. The MRF contained the protocol, manual of operations, all case report forms, all site IRB approvals, minutes and recommendations from all DSMB meetings, minutes of all study committee meetings, state licensures for all investigators and coordinators (nurses), certification for laboratories, pharmacies, and radiology departments, information about the investigational product, drug destruction logs, and all reports from the final monitoring visits of the sites. This file was sent to the NIDDK and all the site principal investigators. The DCC also created site-specific reports on recruitment, protocol adherence, serious adverse events, and outcomes assuming the sites would need this information for IRB closeout and future research endeavors.

Data Sharing and [Clinicaltrials.gov](https://www.clinicaltrials.gov)

The HALT PKD investigators were required to share deidentified study data and results through the NIDDK data repository (<https://www.niddkrepository.org/home/>) and www.clinicaltrials.gov, respectively. Multiple levels of data sharing involved trial documentation, case report form (CRF) data, non-CRF data (laboratory sample results and imaging), publications, publication datasets, and complete datasets with all data. The amount of effort to support this activity should not go underestimated. We covered approximately 50% of a Masters-level statistician to create the CRF and non-CRF SAS datasets, documentation, and analysis datasets (with programs) for all of the data that were shared. Baseline data was shared in early 2014 prior to the closing of the trial along with the validated program that ran analyses presented in the HALT baseline paper.[10] The NIDDK data repository sharing process involves a simple upload to a password protected FTP site instead of tapes or disks.[4] The forms data, analysis datasets and programs for the primary papers[12, 13] were shared within 6 months of the primary publications. All trials are required to be registered with www.clinicaltrials.gov and report results within 1 year of the close of the study. Study A and Study B were initially registered as one trial (NCT00283686) but in preparation for closeout, the DCC decided to separate the two trials due to the different types of designs (2×2 factorial versus traditional two-arm parallel) and different types of primary outcomes (continuous with repeated measures versus time-to-event). The DCC completed all entry of results with approval by NIDDK and the [clinicaltrials.gov](https://www.clinicaltrials.gov) review prior to the 1 year deadline, a goal met by only 14% of trials registered.[18] Meeting this timeline would not have been possible without the rigorous activities that occurred to prepare for the primary trial result publications. By reviewing the guidance[19] and online modules, we encountered relatively few challenges when we entered the results of our trials into the Protocol Registration and Results System of www.clinicaltrials.gov. Our major challenge was the time it took to enter the longitudinal data for our primary outcome and 6 secondary outcomes in the form of slopes (annual change) for both studies, particularly Study A which was a 2×2 factorial trial. Fortunately for the adverse events, [clinicaltrials.gov](https://www.clinicaltrials.gov) has an upload option for spreadsheets that have

collapsed frequency data for serious adverse events by organ system and event term (number of events, number of participants affected). All trials (including trials of non-pharmacological interventions) should use common classification systems for adverse events such as the Common Terminology Criteria for Adverse Events (CTCAE)[20] or MedDRA[21] to ease the effort needed to report the safety profiles of the interventions in a trial.

Discussion

Planning for closeout just two years prior to the last patient visit was an extremely difficult task. Study wide, we observed a major misconception about the effort needed to close down our studies with the belief that patients winding down would correlate with less human effort to support the trials. We provide our experience as lessons learned so that others will not confront what were sometimes last-minute, reactionary decisions with the quickly impending deadline of study end. Our planning, albeit late in the trial, made a significant impact on to ensure patient safety and dissemination of results. Tapering of medications was a primary issue requiring detailed documentation, training, modification of the research database for additional data collection, and significant staffing for follow-up. We successfully had no participants experience any serious adverse events related to tapering. We were able to quickly disseminate study results to the public and scientific community through a conference press release, the *NEJM* online publications, and the PKD Foundation website within 6 weeks of database lock. Participants received their allocation and results within 1–3 months after the public release. In less than 9 months from the last visit, the DCC had fully met all repository and reporting obligations.

One critical issue that we could not fully prepare for [7] was the departure of 6 of 13 lead coordinators to retirement or other research positions, some of whom had been on the study since initiation. The site teams adapted by hiring new coordinators or reallocating time for staff from other projects largely for non-patient related tasks. The high staff turnover did not impact patient follow-up. The lowest rate of follow-up for penultimate visits was 88% in one site with lead coordinator turnover but this site had 98% follow-up for the final visits. All other sites maintained high follow-up rates for both visits (91%–100%). In addition, successful closeout was facilitated by the patients' commitment to the study.

The amount of work during closeout increased significantly in order to assure issues with patient communication, patient safety, and compliance were addressed in a timely fashion. The last patient visits spanned across 6 months for all sites but ultimately the sites' closeouts occurred simultaneously during 3 months prior to database lock. The most difficult tasks stretching site resources (even those sites who did not lose staffing) were the 8 week follow-up calls and data entry for all participants, the thorough review of each participant's study charts (Milestone One of site closeout), and the culmination of all documents for uploading into the Master Regulatory File. The DCC held regular calls with the study teams to monitor for problems. As a result, the DCC lead nurse coordinator and project manager made several trips to sites to provide training for new staff and substantial assistance with closeout activities. Fortunately, these trips had been expected based on work by others [6] so the DCC made budgeting accommodations. Risk-based monitoring and central statistical monitoring

have received increased attention where efforts focus on risks to the “most critical data elements and processes necessary to achieve study objectives” [22] and identifying problem sites[23, 24]. We centrally monitored data quality on a monthly basis for trial endpoints, centrally processed lab samples, serious adverse events, and drug disposition. In the last few years of the trial, we generated numerous data quality reports for sites focusing on measurement of primary and secondary outcome. Even with central monitoring, the final monitoring visits by the DCC for all sites were necessary to emphasize clinical investigator responsibilities and sponsor expectations, to assist site teams with closeout activities, and to reinforce timelines of outstanding milestones. The need for these resource intense on-site visits could be decreased with availability of remote access to sites’ essential documents and electronic health records, virtual meetings, and trial management systems particularly if a site has an experienced investigative team and no performance issues.

The DCC efforts to clean data, run analyses for primary papers, and comply with data sharing were only possible because of the financial resources for the DCC. In our experience, data management and analyses for smaller trials are highly under resourced to comply successfully with data sharing responsibilities. We strongly encourage investigators applying for NIH funding to not dismiss the amount of effort needed to comply with NIH policy on data sharing of final research data for funded projects of \$500,000 or more in direct costs (http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.Htm, Accessed March 26, 2015). We would suggest at least 0.5 FTE of a Masters level statistician and at least 0.25 FTE of another statistician and a systems analyst in collaboration with the study statistician to ensure the files shared are fully documented and verified for broad dissemination and reproducibility.

Although our closeout was successful, we recommend planning much earlier in a trial, possibly during the development of the manual of operations particularly for double-blind, placebo controlled trials. The penultimate visit questions pertaining to unblinding and study results should occur during the informed consent process of the study with a default of providing this information to participants at the end of the study and only if they opt out would their data not be provided to them. Shepherd et al[3] has suggested the study protocol stipulate planning for closeout before or just after the first participants are randomized with the goal of final plans prior to the first interim analysis. If investigators can plan closeout earlier, they can fully budget to support regular study activities, training, drug supplies and storage, and closeout activities. With respect to dissemination, having the national conference as a “hard deadline” allowed us to establish timelines for writing of the manuscript critical in the quick dissemination of the trials’ results. Both trials had negative findings with respect to the impact of double blockade of the RAAS so having all investigators in agreement as to when the drafts would be circulated kept the writing focused and the co-authors committed. We recommend planning a strict publication timeline for any trial to minimize delay in improving patient care and improve the rate of scientific evidence-building based on the gold standard of study designs.

When designing closeout, trial investigators must consider issues that have an impact on the design of the trial, the safety of participants, the cost of implementation, and the timeliness of dissemination. We suggest they consider the following questions for guidance:

1. Participant level:
 - a. What is the last visit for a participant? Is it a fixed, structured time point relative to baseline (such as 3 years from baseline) or the last expected visit before the end of the trial?
 - b. Does the participant need to be tapered off drug?
 - c. What activities will occur at the last visit outside of normal study visits?
 - d. What length of follow-up, if any, is needed for safety?
 - e. In a double-blind study, when and how will allocation information be provided to the participant? If possible, add this to the consent documentation.
 - f. When and how will study results and individual results be provided to the participant and their primary care provider? If possible, add this to the consent documentation.
2. Site level:
 - a. What are the major milestones for closeout pertaining to participants, drug inventory, and biological samples?
 - b. Are resources available for full staffing during and immediately after participant closeout?
 - c. Are team members aware of others roles and able to take on other responsibilities during closeout?
 - d. Are research units such as clinical research centers, pharmacy, laboratories, and imaging facilities aware of closeout and are special procedures required?
 - e. Are all regulatory documents stored in a secure location on a network available to study personnel?
 - f. What are the site policies for retention of study documents after study end?
3. DCC level:
 - a. Do any special procedures at the last patient visits require modified or additional data collection?
 - b. Does the DCC have open communication with sites and a data monitoring plan to detect problems during closeout?
 - c. Can a timeline be established for database lock, primary analyses programming and validation, and drafting of the primary result manuscript? Who will lead the writing team? What is the author order?
 - d. What are the data sharing requirements by the sponsor? What data sharing activities could start earlier prior to the last participant follow-

up? What is the timeline for fulfilling the remainder of the data sharing responsibilities?

- e. Who is responsible for clinicaltrials.gov reporting? Can baseline results be entered early? Has anything changed since the study was first entered into clinicaltrials.gov that needs revision?
- f. What reporting is required to the FDA and industry sponsor for studies involving investigational agents and devices? When are the reports needed?

Finally, we recommend that a very detailed timeline of study events be maintained by the DCC during the closeout period (1–2 years prior to the last patient visit). The important things that happen such as staff changes, committee decisions, and external influences on the planned closeout activities will be forgotten. These details will be critical for planning closeout of the next trial.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Overview of HALT PKD trials with interventions, outcomes, timeframes, and organizational structure.

DATE:

Dear (Participant's Name),

The Investigators of the HALT-PKD clinical trial wish to inform you that the study officially concluded June 30, 2014. Over the past several months the analysis of all data has taken place and a summary of the study results is now available.

During your last study visit, you indicated a desire to receive information on your treatment allocation during your participation in the study. The information supplied to you in this letter will also be shared with the local physician that you identified during your last study visit.

During your study participation you were assigned to the following treatment group:

Study arm assignment: _____

We have completed a review of your lab and radiology data obtained during your participation. The information below reflects those measures:

Date of study enrollment:	_____	
Date of final study contact:	_____	
Estimated GFR at enrollment:	_____	Date: _____
Estimated GFR at last visit:	_____	Date: _____
Total kidney volume MRI #1:	_____	Date: _____
Total kidney volume final MRI:	_____	Date: _____
Current Kidney disease staging:	_____	Date: _____
Blood Pressure Measurement:	_____ / _____	Date: _____

Enclosed for your review, please find a copy of published study results recently provided to our sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). If you have questions or concerns with any of the information please contact your study investigator, Dr. _____ at: _____.

The HALT-PKD study is one of the largest ADPKD studies ever done. We are hopeful that the study results will be beneficial for millions of PKD patients worldwide. Thank you for your dedication to the HALT-PKD clinical trial. Your participation in this endeavor has been invaluable in assisting our understanding of this disease and how best to treat it.

Sincerely,

[Investigator]

Figure 2.
Participant Study Results Letter

SEQUENCE OF PATIENT VISITS and NOTIFICATION LETTERS for CLOSEOUT

Figure 3.
Notification Letters for Closeout

Figure 4.
Study Timeline

Table 1

Questions from Next to Last Visit Questionnaire

1) During today's visit, did you complete the HALT-PKD study FORM #2- "Contact Information Form"?
2) Do you have a PCP or nephrologist identified for the HALT-PKD team to transition your care to in six months? 2a If no or unsure, do you have access to an alternative care center or clinic? Please provide that contact information to your coordinator.
3) When the study comes to an end, will you have established insurance, Medicaid or Medicare coverage? 3a If no or unsure, do you plan to apply for Medicaid or Medicare coverage? If so, please start the application process within the next two weeks.
4) Once the study results are released, your HALT PKD investigator, depending on your response below, will send you, and the physician you identified on Form #2, a letter containing your basic study information gathered over the course of the study. This letter will provide your lab results (kidney function-eGFR), radiology results (total kidney volume on MRI-Study A only), current stage of kidney disease, blood pressure measurement and your study treatment assignment (either telmisartan or placebo). 4a Do you want to receive your study results information? 4b Do you give the HALT PKD study permission to share your study results with your local physician(s)?
5) Do you want to be told what study arm (telmisartan or placebo) you were assigned to during your participation? 5a Do you give the HALT PKD study permission to share your treatment allocation (telmisartan or placebo) with your local physician?
6) Please identify the physician or designated provider that is to receive the final study letter.
7) How would you like us to send the final study letter to you?