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The transitioning from trials to extended follow-up studies

Lea T. Drye, Anne S. Casper, Alice L. Sternberg, Janet T. Holbrook, Gabrielle Jenkins, and
Curtis L. Meinert

The Johns Hopkins University, Bloomberg School of Public Health, Department of Epidemiology,
615 North Wolfe St, Baltimore, MD21205

Abstract

Background—Investigators may elect to extend follow-up of participants enrolled in a randomized clinical trial after the trial comes to its planned end. The additional follow-up may be initiated to learn about longer term effects of treatments including adverse events, costs related to treatment, or for reasons unrelated to treatment such as to observe the natural course of the disease using the established cohort from the trial.

Purpose—We examine transitioning from trials to extended follow-up studies when the goal of additional follow-up is to observe longer term treatment effects.

Methods—We conducted a literature search in selected journals from 2000–2012 to identify trials that extended follow-up for the purpose of studying longer term treatment effects and extracted information on the operational and logistical issues in the transition. We also draw experience from three trials coordinated by the Johns Hopkins Coordinating Centers that made transitions to extended followup: the Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT); Multicenter Uveitis Steroid Treatment (MUST) trial; and Childhood Asthma Management Program (CAMP).

Results—Transitions are not uncommon in multicenter clinical trials, even in trials that continued to the planned end of the trial. Transitioning usually necessitates new participant consents. If study infrastructure is not maintained during the transition, participants will be lost and re-establishing the staff and facilities will be costly. Merging data from the trial and follow-up study can be complicated by changes in data collection measures and schedules.

Limitations—Our discussion and recommendations are limited to issues that we have experienced in transitions from trials to follow-up studies.

Discussion—We discuss issues such as maintaining funding, IRB and consent requirements, contacting participants, and combining data from the trial and follow-up phases. We conclude with a list of recommendations to facilitate transitions from a trial to an extended follow-up study.

Keywords

linical trial; transitioning; morphing; extended follow-up

Introduction

Trials are dynamic organisms. Their form or character can change while underway as a result of protocol revisions, e.g., as with the addition or deletion of a study treatment or change in dosage schedule of a treatment, and such changes may prompt investigators to decide to extend follow-up of participants after the trial period of the study ends.

Alternatively, the prompt for additional follow-up of a trial's participants may derive from events or research subsequent to termination of the trial. Thus, transitions may be seamless with participants moving to follow-up as the trial ends or may take place months or years after the trial has finished, e.g., as in mortality follow-up of people enrolled in the Coronary Drug Project or in the Multiple Risk Factor Intervention Trial.^{1,2} Depending on the purpose and resources available, the follow-up may be by direct contact, with participants being followed at the original study clinics, by telephone or letter, or without any direct contact (e.g., in the case of mortality follow-up via death indices).

Factors causing investigators and sponsors to transition from trial to follow-up include interest in the long-term effects of treatments administered in the trial; characterizing disease progression in persons studied in the trial; characterizing frequency of adverse events after cessation of the trial; or characterizing mortality following cessation of the trial. The likelihood of transition to follow-up depends on identifying a worthwhile scientific question that can be answered by additional follow-up; a sponsor or funder willing to pay for the follow-up; investigators willing to do the follow-up; feasibility of locating and collecting data on persons enrolled in the trial and their willingness to continue; and size and uniqueness of the original study population.

Although many trials extend follow-up after the trial period ends, not much has been written about the issues that are encountered. We have experienced transitioning in three trials coordinated by the Johns Hopkins Coordinating Center and our goal is to review related transitions in the literature and to comment on our own experience.

Methods

Identifying trials from literature search of selected journals and personal experience, we describe trials that have transitioned to extended follow-up with the primary goal of comparing long-term treatment effects.

Literature Search

We searched PubMed for articles from the New England Journal of Medicine, BMJ, Journal of the American Medical Association, Lancet, and Annals of Internal Medicine with publication dates between 2000 and 2012 and reporting on recent multicenter trials that have undergone this transition. The search was not meant to be representative of all literature published but to provide insight into issues encountered during transitions and strategies for resolution. The search targeted publications including any of the following terms (the search strategy is detailed in the Appendix 1):

- additional follow-up;

- continuation study;
- extended follow-up;
- extended observational period;
- legacy;
- long-term effect;
- post-trial;
- follow-up study.

Articles identified by the aforementioned search terms (as of 04Apr2013) were then reviewed (AC with review of questionable results by LD) to determine if the results reported were from follow-up of a previously identified population enrolled and followed in a clinical trial. To limit the results to those transitions that were similar to our experience, we included only those trials and follow-up studies meeting the criteria shown in Table 1.

Trials conducted at Johns Hopkins Coordinating Centers

At the Johns Hopkins Coordinating Centers, several trials have transitioned to extended follow-up. We examine three trials that transitioned to extended follow-up in order to compare long-term treatment effects by the original treatment groups: Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) to ADAPT Follow-up Study (ADAPT-FS); Multicenter Uveitis Steroid Treatment (MUST) trial to MUST Follow-up Study (MUST-FS); and Childhood Asthma Management Program (CAMP) to CAMP Continuation Studies (CAMPCS). The study protocols were reviewed and approved by the ethics committee at each clinical center and the coordinating center for these trials and follow-up studies.

ADAPT and ADAPT-FS—The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) was designed to address whether non-steroidal anti-inflammatory drugs can prevent or delay the onset of Alzheimer disease.³ It was a randomized, placebo-controlled, prevention trial conducted at six U.S. dementia research clinics. At entry, participants were required to test "normal" on a battery of cognitive tests and to be age 70 or older with a family history of dementia. Persons were randomly assigned to 200 mg b.i.d. celecoxib (Celebrex®), 220 mg b.i.d. naproxen sodium (Aleve®), or placebo. ADAPT was funded by the National Institute on Aging. The primary outcome measure was diagnosis of Alzheimer disease. Secondary outcome measures were cognitive decline and measures related to safety of the treatments when used long term. A total of 2,528 people were enrolled from March 2001 through mid- December 2004. Treatments were suspended in mid-December 2004 due to concerns regarding cardiovascular safety of the treatments.⁴

ADAPT follow-up of participants off treatment continued through the end of February 2007 (mean follow-up of 3.2 years). Patients and investigators were unmasked to treatment assignment from May to July of 2007 prior to the cessation of funding for clinics in the fall of 2007. An analysis of the ADAPT trial suggested that the effects of naproxen on the incidence of Alzheimer disease changed over time, with an increase in risk observed in approximately the first two years after randomization with a decreasing risk thereafter.⁵

Given the lack of available trial data on the long-term effects of non-steroidal antiinflammatory drugs on cognitive function, the investigators judged it necessary to extend follow-up of the cohort to learn whether the emerging trends in effects on incident Alzheimer disease continued. Funding for additional follow-up was obtained in the second half of 2009, and participants in ADAPT were recontacted in 2010 for participation in ADAPT-FS.

Ultimately 1537 people were enrolled for extended cognitive follow-up in ADAPT-FS⁶ and record of death was obtained through death searches for an additional 134 participants. Follow-up in ADAPT-FS was completed at the same clinical centers where ADAPT was completed. Figure 1 displays the timeline for ADAPT and ADAPT-FS.

MUST and MUST-FS—The Multicenter Uveitis Steroid Treatment (MUST) Trial, funded by the National Eye Institute, compared the fluocinolone acetonide implant (Bausch & Lomb, Inc., Rochester, NY) to systemic therapy with oral corticosteroids supplemented by immunosuppressive drugs when indicated for patients with severe noninfectious intermediate uveitis, posterior uveitis, or panuveitis.⁷ A total of 255 patients were randomized between December 2005 and December 2008.

The MUST Trial was designed to provide at least two years of follow-up on participants and MUST Trial 2-year results have been published.⁸ The two treatments produced similar improvements in visual acuity. There were fewer participants experiencing uveitis activity and more reported improvement in vision-related quality of life in the implant group but also a higher incidence of ocular complications such as cataract and glaucoma.⁸ Because intermediate, posterior or panuveitis is usually a chronic disease and the implants were designed to last 2.5 to 3 years, the investigators felt that continued follow-up of the MUST cohort would provide data on long-term treatment effectiveness and safety.

In MUST-FS participants from the MUST Trial are being followed for five additional years and are encouraged to continue with their MUST Trial assigned treatments for uveitis control. Investigators used funds from the MUST Trial to fund the transition from MUST Trial to MUST-FS. There was no lapse in funding between MUST Trial and MUST-FS.

MUST-FS enrolled 215 participants from MUST Trial. The data collection schedule changed from every 3 months in the trial to every 6 months in MUST-FS which introduced challenges for data merging and analysis. Figure 2 displays the timeline for MUST Trial and MUST-FS.

CAMP and CAMPCS—The Childhood Asthma Management Program (CAMP) was a randomized, double-masked, placebo-controlled trial conducted at eight North American clinical centers comparing the efficacy and safety of 400 µg/day of budesonide, 16 mg/day of nedocromil, and matching placebo in children with mild-to-moderate asthma.⁹ CAMP was funded by the National Heart, Lung, and Blood Institute. A total of 1041 children ages 5 to 12 were randomized to treatment between December, 1993 and September, 1995 and followed for a mean of 4.3 years.¹⁰ The CAMP results showed that neither budesonide nor nedocromil were superior to placebo with respect to lung function but that budesonide

improved airway responsiveness and asthma control. However, children in the budesonide group had a small reduction in mean height compared to the other two groups at the end of the trial.¹⁰ The CAMP investigators wanted to continue to follow-up the children to see if the years of treatment in CAMP had any lasting effect on asthma control or height at adulthood after discontinuation.

A study medication washout phase was completed in March through October 1999. Children continued to use asthma medications prescribed in supplement to CAMP study medication. Beginning in November 1999, participants were enrolled into the CAMP Continuation Study (CAMPCS) during which the children's asthma was managed by their asthma care provider and the asthma medications prescribed could include the study medications (budesonide and nedocromil) which had been approved by the FDA during the trial.

Follow-up under CAMPCS continued from November 1999 through March 2012, in three funding phases. Each phase included at least one annual in-person visit at the CAMP clinical centers.^{11,12} More than 85% of the original CAMP enrollees continued in at least one of the follow-up study phases, and 80% participated in all three of the follow-up phases. Figure 3 displays the timeline for CAMP and CAMPCS.

Results

Literature search

345 articles were identified with the PubMed search criteria. A total of 17 trials (16 corresponding follow-up studies) met our inclusion criteria for this discussion; the Observational follow-up of the Trials of Hypertension Prevention follow-up study enrolled participants from two trials (TOHP I and II). Table 2 gives details regarding the extended follow-up studies.

Twelve of the 17 trials had primary or secondary prevention outcomes and included healthy participants or individuals with certain risk factors for a specific disease or condition: Women's Health Initiative Hormone Therapy Trial¹³ and Heart Protection Study¹⁴ for prevention of cardiovascular events; United Kingdom Prospective Diabetes Study,¹⁵ Diabetes Control and Complications Trial,¹⁶ Finnish Diabetes Prevention Study¹⁷ and the China Da Qin Diabetes Prevention Study¹⁸ for prevention of complications of diabetes; Overview of the Role of Antibiotics in Curtailing Labour and Early delivery I¹⁹ and Overview of the Role of Antibiotics in Curtailing Labour and Early delivery II²⁰ for prevention of adverse neonatal outcomes with preterm rupture of membranes or preterm labor; Trials of Hypertension Prevention I²¹ and II²² for prevention of hypertension; Diabetes Prevention Program for prevention of type 2 diabetes;²³ and Long-Term Intervention with Pravastatin in Ischemic Disease for the prevention of cardiovascular events and mortality.²⁴ The remaining five trials were treatment trials: CAMP compared treatments for childhood asthma;⁹ a trial of treatment strategies for postnatal urinary and faecal incontinence;²⁵ Multicenter Study of Hydroxyurea in Sickle Cell Anemia compared treatments for sickle cell anemia;²⁶ a trial comparing medical and surgical therapies for gastroesophageal reflux disease;²⁷ and a trial testing fatty acid supplementation in infant formula.²⁸ Eight of the trials corresponding to the follow-up studies in Table 2 consisted of

only drug interventions,^{9,14,16,19,20,24,26,28} five consisted of only behavioral interventions,^{17,18,21,22,25} three were a combination of both drug and behavioral interventions^{13,15,23} and one compared drug and surgery interventions.²⁷ No trials of devices or biologics met our criteria for inclusion mostly because we required repeated treatment administration for inclusion. Most of the trials were primarily funded by government resources,^{9,13–23} one was funded mainly by a non-profit research center,²⁵ and two were funded by an industry funder;^{24,28} some trials had multiple funding sources. The average length of follow-up time during the original trials is between 3 and 4 years.

Thirteen trials continued all treatment arms to their planned end. In the Women's Health Initiative Hormone Therapy Trial, the estrogen plus progestin arm was stopped in 2002²⁹ and the estrogen alone arm was stopped in 2004,³⁰ because of evidence that the overall risk to participants' health exceeded the benefit of the hormone therapy. In the Finnish Diabetes Prevention Study, the Endpoint Committee recommended ending the trial ahead of schedule because the interim analysis conducted in March 2000 showed that the cumulative incidence of diabetes was significantly lower in the lifestyle intervention than the control group.^{31,32} The blinded treatment phase of the Diabetes Prevention Program was stopped a year before the planned end because the superiority of both the lifestyle intervention and metformin was established.³³ The Long-Term Intervention with Pravastatin in Ischemic Disease trial was also terminated early with evidence of survival benefits.³⁴

The purpose of each extended follow-up study listed in Table 2 was to gather information on the long-term effects of the treatments that might have appeared after the trial ended, including duration of any effects observed during the treatment period, emergence of new effects, and waning or intensification of effects. During the extended follow-up periods, there was no additional randomization to treatment and participants might receive standard of care treatment, continue on their study treatment under open label, non-study prescription, or receive no treatment at all, depending on their own preference or need and their primary care provider's judgment. Eight studies had periods of time or gaps between the close of the original trial and initiation of extended follow-up;^{35–43} these gaps ranged from two years^{36,37} to 10 years.³⁹

During the follow-up study, the data collection responsibilities appear to have shifted to a central facility (coordinating center) instead of the original recruiting centers in five of the studies,^{36–40,44} with the follow-up primarily conducted through mailed questionnaires and/or telephone contacts. The recruiting clinics continued to perform data collection at in-person visits for the remaining follow-up studies.^{10,32,34,35,41–43,45–48}

Issues encountered in ADAPT, MUST and CAMP transitions

Obtaining funding—Given the huge investment made in the original trial, funders frequently have an interest in repurposing the trial's resources (investigators, participants, and infrastructure) to obtain additional results and hence may have an interest in supporting a follow-up study of the trial participants. But at times the desire or resources from the original funder have disappeared and investigators must find funds elsewhere. In ADAPT, early attempts to obtain funds for additional follow-up from the National Institute on Aging were unsuccessful. The investigators then sought and received funding from a non-profit

organization for the follow-up data collection. Eventually, additional funding was also received from the National Institute on Aging through the American Recovery and Reinvestment Act.

When funding is provided, it is frequently reduced relative to the trial level. In ADAPT-FS, funding reductions required a change in data collection methods so that regular visits to assess cognition were conducted over the phone and in-person visits only occurred when a participant triggered a more thorough dementia examination. The funding for MUST-FS was less than half of MUST Trial funding resulting in fewer study visits (every 6 months instead of 3 months) and a sharp reduction in ancillary testing. Funding for the CAMP Continuation Study phases was reduced compared to the trial phase. The CAMPCS visit schedule included fewer in-person visits per year, the patient education center established for the CAMP trial was not continued in the follow-up phase, and the frequency of some clinical assessments was decreased in the follow-up phase (e.g., home dust collection was not completed in the follow-up phase and psychological assessments were more limited in the follow-up phase). Staffing levels in the extended phases for ADAPT, MUST, and CAMP were reduced compared to the trial phases, in accordance with these changes and reductions in study activities. While some loss of staff with experience and knowledge of the trials was experienced by each study, the effects were mitigated by reassigning staff where possible to other studies being conducted within the research group so that staff were available, when needed, for the follow-up studies.

Transition period—The period of transition between the trial and the follow-up study might be seamless in that participants exit the trial and enter the follow-up study without any gap in their contact schedule, whereas other transitions involve periods of time during which the trial has closed and the follow-up study has not opened. The MUST research group was able to design the follow-up study and obtain funding so that the original cohort could be followed without interruption. During this transition period between the MUST Trial and MUST-FS, participants at some clinical centers were followed under the MUST Trial protocol for a longer period of time than others while IRB approval for the MUST-FS was obtained. The study website, forms and data entry systems had to accommodate both MUST Trial and MUST-FS data collection requirements simultaneously. The CAMP research group was similarly able to obtain funding to transition seamlessly from trial to follow-up without interruption.

In ADAPT, funding for the trial ended before funding could be secured for continued follow-up so participants had to be closed out of the trial. The lapse introduced multiple difficulties and inefficiencies: establishing a new infrastructure, hiring and training new staff due to turn-over during the lapse, submitting new protocols through IRBs and finding participants who had been out of contact with study staff.

Consent—The first issue related to consent in follow-up studies is whether re-consent for the additional follow-up is necessary. Most IRBs require specific language about how long participants will be asked to participate and who will contact them, making it unlikely that the consent for the trial will be adequate for the additional follow-up. If language in the original consent was not specific about follow-up time then it might be sufficient for the

extended follow-up. Follow-up for vital status via searches of the National Death Index or Social Security Death Master File may be possible without additional permission from the patient.

Changes in study organization, protocol, or procedures that occur between the trial and follow-up will likely mandate re-consent. We had to consent participants for the ADAPT-FS, MUST-FS, and CAMPCS because the trial consents were specific to the trial's goals, follow-up period, methods of contact, visit schedules and treatment, and were deemed not to cover the purpose, procedures etc., of the additional follow-up.

In ADAPT-FS, the coordinating center prepared a letter that clinic staff mailed to the last known address of each participant; the letters explained the rationale and methods of the follow-up study, informed the participants that they would be contacted by phone soon, and provided clinic contact information in case of questions before the telephone call. During the telephone contact, coordinators reiterated information about the follow-up study and asked the participant if he/she would be willing to do a telephone cognitive assessment (oral consent) and make an in-person visit, if necessary, to the clinical center. If an in-person visit was triggered due to cognitive difficulties detected during the telephone assessment, the patient was asked to schedule a clinic visit.

A more detailed and written consent was collected at that visit. An option that can ease the transition but will require IRBs approvals is to create a file collecting participant contact information at a central facility such as the coordinating center before the trial ends. Creation of the file will not be possible if the trials consents state that participants' names and addresses will not be transmitted to the coordinating center or other central facility. Absent such a central file, the only possible route of contact with participants is via study clinical centers. Even when the trial is ongoing, the absence of an identifier file in the coordinating center may be problematic. For example, that absence meant that the coordinating center in ADAPT could not assist clinics in preparing mailings to participants during the close of ADAPT to inform them of treatment assignment. Likewise, mortality sweeps at the end of ADAPT-FS using the National Death Index or Social Security Death Master File had to be done at the clinical centers. Once a trial has finished and the investigator group has disbanded there is no viable means for mortality follow-up without a central file of identifiers.

Finding study participants—The ADAPT-FS, MUST-FS, and CAMPCS investigators attempted to follow as many of the trial participants as possible and did not allow enrollment of non-trial participants in their follow-up phases. There are other models of transitioning that will not be discussed such as one where a trial ends and extended follow-up begins with a combination of trial participants and new participants not involved in a trial (e.g., the Longitudinal Studies of the Ocular Complications of Acquired Immunodeficiency Syndrome).⁴⁹

If there is a lapse in funding between the trial and the follow-up, like in ADAPT, re-contacting participants becomes more difficult. In ADAPT-FS, personal identification, including addresses, was stored only at the clinical sites so follow-up could not be

performed centrally by the coordinating center. Follow-up was performed instead at the original clinical centers starting with the distribution of an introductory letter. After the letter, study staff attempted to contact participants at the last known address recorded during ADAPT. If not successful in contacting the participant, clinical center staff would attempt to call the participant's collateral respondent, friend, or family members listed in ADAPT records and, if necessary, check current telephone directory for listings both for the participant and the participant's contacts. Participants who were contacted were asked to provide an assessment over the phone and if they agreed, they were enrolled in ADAPT-FS. Staff from the clinical centers performed death searches to determine vital status for all ADAPT participants who were not contacted for ADAPT-FS which included those that were eligible and could not be found ($n = 302$), but also those that refused further contact during ADAPT ($n = 65$) and those that were diagnosed with dementia during ADAPT (an additional $n = 66$).

For seamless transitions between trial and follow-up studies, participants can be asked at a trial or transition visit or contact whether they would be willing to continue extended follow-up. For example in MUST, a letter was mailed to trial participants prior to the start of the final round of trials visits explaining the impending transition to follow-up. An additional letter was sent subsequently to inform participants of the MUST trial results with instructions to contact study staff to discuss the results. At the next MUST visit, the participants willing to continue in MUST-FS were consented and scheduled for their first MUST-FS visit.

In CAMP, consent was obtained at the start of each new phase of follow-up. At the last visit of each phase, coordinators spoke with parents and participants about the planned next phase of follow-up, either obtaining consent for the new phase (if logistics permitted) or providing written material about the new phase and obtaining permission to contact the family (or participant if the participant had reached the age of consent) once the new phase had opened. At the start of the trial, CAMP participants were age 5–12 and consent was provided by the parent or guardian. Starting with the first follow-up continuation phase, CAMPCS participants began to reach the age of consent and were asked to provide consent to the follow-up. CAMPCS continued long enough so that all of the participants had entered adulthood by the start of the third continuation phase. Investigators discovered that interest or disinterest in participation was not static. Teens or college students might not be interested, but young adults who were on their own or were new parents often rekindled their interest in CAMP. At the end of the trial, participants were provided with a personalized summary of their own measurements and test results over the duration of the trial; during the continuation phases, brief updates on CAMP contributions to asthma care were provided to reinforce the bond with CAMP.

Outcome measures—The outcome measures of the follow-up phase depend on the goal of continued follow-up. Care should be taken to make sure outcomes are collected in such a way that the data from the trial and follow-up study can be combined. This is easier said than done when there is pressure to “improve” the data collection because of changes in technology of measurement from the time of the trial to follow-up. Minor wording changes

in data items common to the trial and follow-up may make comparison across the two components of study problematic.

In ADAPT, an analysis of treatment effects over time suggested that the naproxen treated group had an increased risk of Alzheimer disease early in the trial (compared to placebo) and a decreased risk in the late years of the trial. The goal of the follow-up was to see if the decreased risk observed late in the trial was sustained.

If there is a gap between the trial and the follow-up study, this can create problems for timing survival outcomes. For example, Alzheimer disease diagnoses that occurred during the period between ADAPT and ADAPT-FS had to be confirmed during ADAPT-FS. As such, the study events for the survival analysis identified during ADAPT-FS had a short window of possible event dates when in reality, the diagnosis dates should have been spread over the several years gap between the ADAPT and ADAPT-FS. This makes it difficult to summarize denominators for presentation and complicates calculation of incidence rates.

In MUST, the primary trial outcome of change in visual acuity from baseline to two years was very similar in the two uveitis treatment strategies, and the follow-up study was designed to continue to collect data on the primary outcome as well as information on long-term safety and treatment costs. The data collection interval changed from three months to six months which caused difficulties in combining some of the outcomes from the trial and follow-up study. The trial results were published with estimates of several outcomes based a three month visit schedule. An analysis testing different intervals (3 month versus 6 months) for statistical analyses of trial data were necessary before combining the trial and follow-up data.

The original CAMP study was designed to compare efficacy of three management strategies for childhood asthma while the follow-up was designed primarily to assess long-term effects of the inhaled corticosteroid treatment, both with regard to lung function and potential negative effects on attained adult height. The last two phases of CAMP follow-up were also designed to address the natural history of mild to moderate childhood asthma which requires different analysis strategies for timing of study events (e.g., timed by age of the child instead of time since randomization). During the CAMP trial, the timeline of interest for analysis of the outcomes was the duration since randomization. In the follow-up studies, the enrollment was spread over a number of years. The visits being completed in a calendar time period represented different durations from randomization. Sensitivity analysis using age as the timeline was a valuable approach during the follow-up studies.

Treatment during extended follow-up study—In ADAPT-FS, the investigators had no reason to offer any of the ADAPT treatments to the participants who continued follow-up since neither of the experimental treatments were found to be effective. MUST found that both treatment strategies provided similar improvements on the primary outcome of visual acuity and most participants experienced good control of uveitis flares. Therefore, investigators are encouraged but not required to continue to provide treatment according to randomized assignment in MUST-FS. At the end of the CAMP trial, participants returned to

their personal asthma care provider for asthma treatment per clinical guidelines; CAMP study physicians sent the provider their recommendations if permitted by the participant.

Limitations

Other issues could arise with transitioning that we did not encounter. Our experiences with ADAPT, MUST and CAMP may not be generalizable to all trials transitioning to extended follow-up because CAMP and ADAPT were trials in populations for whom it may be markedly difficult to continue follow-up, (i.e., children and older adults) and our experience focuses on trials conducted primarily in the United States. In addition, other types of transitions, such as those where the investigators enroll new participants during the follow-up period, those that only follow a subset of originally enrolled participants or those that collect data only through registries (no participant contact), will have other issues not covered here.

Discussion

It is not uncommon for trials to transition to an extended follow-up period. This transition occurs in prevention and treatment trials, trials enrolling children and adults, trials funded from many sources and those testing a variety of interventions. The reality is that transitions from trial to follow-up study are usually after thoughts. That being so investigators can expect to face a variety of problems and issues if they elect to engage in some form of follow-up after the trial is finished. In table 3 we have included some recommendations on how to make extended follow-up more feasible based on our experience from ADAPT, MUST and CAMP.

Our primary recommendation is to plan ahead. Just as good design includes features to protect against Type I error, deviations from assigned treatment, loss to follow-up of participants, so might the trial designer build in some insurance in case the trial results leave an important question dangling. Consider designing a consent that leaves the door open to further contact, try to use data collection procedures that will work in the future, and always think about what should be done now to ensure the most options later.

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Appendix 1 Literature review search strategy

PubMed search date: 04Apr2013

Search	Query	Items found
#1	Search ("additional follow-up" OR "extended follow-up" OR "continuation study" OR "extended observational period" OR "legacy" OR "long-term effects" OR "post-trial" OR "follow-up study")	52640
#2	Search ("The New England Journal of Medicine"[Journal]) AND ("2000/01/01"[Date - Publication] : "2012/12/31"[Date - Publication])	18165
#3	Search ("BMJ"[Journal]) AND ("2000/01/01"[Date - Publication] : "2012/12/31"[Date - Publication])	30093
#4	Search ("Lancet"[Journal]) AND ("2000/01/01"[Date - Publication] : "2012/12/31"[Date - Publication])	23854
#5	Search ("JAMA"[Journal]) AND ("2000/01/01"[Date - Publication] : "2012/12/31"[Date - Publication])	14659
#6	Search ("Ann Intern Med"[Journal]) AND ("2000/01/01"[Date - Publication] : "2012/12/31"[Date - Publication])	7282
#7	Search (#1 AND #2)	56
#8	Search (#1 AND #3)	79
#9	Search (#1 AND #4)	110
#10	Search (#1 AND #5)	62
#11	Search (#1 AND #6)	38

Manuscript ID:	CT-13-0269.R1													
Funding Information:	No funding details provided													
Submitting Author:	<div> <input type="text" value="Drye, Lea T."/> ☒ Save <input type="button" value="Drye, Lea T. (proxy)"/> </div> <hr/> <p> <i>* primary affiliation</i> Johns Hopkins School of Public Health - Epidemiology 911 S Ann St Baltimore Maryland 21231 United States T: 443-287-3170 F: 443-287-5797 </p>													
Authors & Institutions:	<table border="0"> <tr> <td> <input type="button" value="Drye, Lea T. proxy"/> </td> <td> <ul style="list-style-type: none"> Johns Hopkins School of Public Health - Epidemiology 911 S Ann St , Baltimore, Maryland 21231 United States </td> </tr> <tr> <td> <input type="button" value="Casper, Anne S. proxy"/> </td> <td> <ul style="list-style-type: none"> Johns Hopkins School of Public Health - Epidemiology Baltimore, Maryland United States </td> </tr> <tr> <td> <input type="button" value="Sternberg, Alice L. proxy"/> </td> <td> <ul style="list-style-type: none"> Johns Hopkins School of Public Health - Epidemiology Baltimore, Maryland United States </td> </tr> <tr> <td> <input type="button" value="Holbrook, Janet T proxy"/> </td> <td> <ul style="list-style-type: none"> Johns Hopkins University - Epidemiology 615 N Wolfe ST W5010, Baltimore, Maryland 21205 United States </td> </tr> <tr> <td> <input type="button" value="Jenkins, Gabrielle proxy"/> </td> <td> <ul style="list-style-type: none"> University of Alabama at Birmingham Ryals School of Public Health - Epidemiology Birmingham, Alabama United States </td> </tr> <tr> <td> <input type="button" value="Meinert, Curtis L. proxy"/> </td> <td> <ul style="list-style-type: none"> Johns Hopkins School of Public Health - Epidemiology 615 N. Wolfe St , Baltimore, Maryland 21205 United States </td> </tr> </table>		<input type="button" value="Drye, Lea T. proxy"/>	<ul style="list-style-type: none"> Johns Hopkins School of Public Health - Epidemiology 911 S Ann St , Baltimore, Maryland 21231 United States 	<input type="button" value="Casper, Anne S. proxy"/>	<ul style="list-style-type: none"> Johns Hopkins School of Public Health - Epidemiology Baltimore, Maryland United States 	<input type="button" value="Sternberg, Alice L. proxy"/>	<ul style="list-style-type: none"> Johns Hopkins School of Public Health - Epidemiology Baltimore, Maryland United States 	<input type="button" value="Holbrook, Janet T proxy"/>	<ul style="list-style-type: none"> Johns Hopkins University - Epidemiology 615 N Wolfe ST W5010, Baltimore, Maryland 21205 United States 	<input type="button" value="Jenkins, Gabrielle proxy"/>	<ul style="list-style-type: none"> University of Alabama at Birmingham Ryals School of Public Health - Epidemiology Birmingham, Alabama United States 	<input type="button" value="Meinert, Curtis L. proxy"/>	<ul style="list-style-type: none"> Johns Hopkins School of Public Health - Epidemiology 615 N. Wolfe St , Baltimore, Maryland 21205 United States
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Contact Author (populates the ##PROLE_AUTHOR_...## e-mail tags):	<div> <input type="text" value="Drye, Lea T."/> ☒ Save </div>	Current Contact Author: Drye, Lea T. (proxy)												
Running Head:	Trials transitioning to extended follow-up													
Keywords:	clinical trial ✖, transitioning ✖, morphing ✖, extended follow-up ✖

Figure 1. ADAPT and ADAPT-FS timeline

*MUST-FS protocol does not dictate which treatment should be used; remaining on the MUST Trial assigned treatment is not required. Ophthalmologists are encouraged to follow MUST Trial treatment guidelines. Most patients elected to remain on their MUST Trial assigned treatment. MUST Trial treatment was not masked to participants.

Figure 2.

MUST Trial and MUST-FS timeline

*MUST-FS protocol does not dictate which treatment should be used; remaining on the MUST Trial assigned treatment is not required. Ophthalmologists are encouraged to follow MUST Trial guidelines. Most patients elected to remain on their MUST Trial assigned treatment. MUST Trial treatment was not masked to participants.

*During a washout period between Mar and Oct of 1999, study treatments were stopped and patients were unmasked; patients completed 2 clinic visits during the washout period. During the continuation studies, participants were treated by their physicians based on National Asthma Education and Prevention Program guidelines which could include CAMP study medication via physician prescription.

Figure 3.

CAMP and CAMPCS (3 phases) timeline

*During a washout period between Mar and Oct of 1999, study treatments were stopped and patients were unmasked; patients completed 2 clinic visits during the washout period. During the continuation studies, participants were treated by their physicians based on National Asthma Education and Prevention Program guidelines which could include CAMP study medication via physician prescription.

Table 1

Criteria for inclusion in literature review

<p><i>Criteria for the original clinical trial</i></p> <ul style="list-style-type: none"> • Phase III/IV (definitive, comparing treatment efficacy or effectiveness) • Individually randomized treatment allocation • Concurrent enrollment and follow-up of treatment groups • Multicenter (multiple recruiting centers) • Designed for study treatment to be administered until study ended • Results published • Began recruitment in 1980 or later <p><i>Criteria for the extended follow-up study</i></p> <ul style="list-style-type: none"> • Additional follow-up period that was not part of the original trial protocol • No randomization to treatment during extended follow-up period • Contacted participants from original trial • Primary objective is to compare original treatment groups • At least one publication of the follow-up study results the New England Journal of Medicine, BMJ, Journal of the American Medical Association, Lancet, or Annals of Internal Medicine between 2000 and 2012
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Table 2

Design features of post-trial follow-up studies

	Post-trial follow-up study	Duration of post-trial follow-up	Timing of trial and post-trial follow-up	Method of data collection	Primary funding source type
1	Women's Health Initiative (WHI) Extension Study	5 additional years follow-up in 2005 to 2010	Continuous, but treatment arms were stopped prior to close of original trial for Hormone Therapy Trial	Questionnaires (health outcomes) annually via mail; phone contacts and medical record review for women reporting study outcomes; mammography reports for Hormone Therapy Trial	Government
2	Childhood Asthma Management Program Continuation Study (CAMPCS)	12.5 additional years in 1999 to March 2012	Continuous	Clinic visits (height, pulmonary function, medical history) every 6 months, with phone contacts between visits, during first 4.5 years observational follow-up and clinic visits 1–2 times a year during the next 8 years	Government
3	UK Prospective Diabetes Study (UKPDS) post trial monitoring	10 additional years in 1997 to 2007	Continuous	Clinic visits with continued standard collection of outcome data until year 5 and then questionnaires until year 10 (transition to questionnaire due to funding limitations)	Government (first 5 years); Pharmaceutical company (second 5 years)
4	Epidemiology of Diabetes Interventions and Complications (EDIC) Study (Follow-up to Diabetes Control and Complications Trial)	8 additional years starting in 1993	Continuous	Clinic visits (glycemic control, renal function, blood pressure, etc.) annually	Government
5	Finnish Diabetes Prevention Study post-intervention follow-up	3 additional years ending in Dec 2004	Continuous	Clinic visits (glucose, labs, physical activity questionnaires, etc.) annually	Government
6	China Da Qin Diabetes Prevention Study	One contact in 2006, 20 years after randomization	Gap (1992 to 2006)	Personal interview, medical records, physical exam, labs (glucose test, ECGs, etc.); death records and relative report	Government
7	7-year follow-up of the Overview of the Role of Antibiotics in Curtailing Labour and Early delivery (ORACLE) I trial	Cohort of 7 year olds starting in 2002	Gap (2000 to 2002)	Parental questionnaire; phone contact for questionnaires not returned; national curriculum test results; UK Office of National Statistics records	Government
8	7-year follow-up of the ORACLE II trial	Cohort of 7 year olds starting in 2002	Gap (2000 to 2002)	Parental questionnaire; phone contact for questionnaires not returned; national curriculum test results; UK Office of National Statistics records	Government
9	Heart Protection Study (HPS) Collaborative Group:LDL with simvastatin	5 years occurring 2001 to 2006	Continuous	Mailed questionnaires annually; follow-up with doctor for those who did not respond (data collection in original trial was clinic visits)	Government
10	Postnatal urinary and faecal incontinence	One contact in 1999, 6 years after randomization	Gap (1995 to 1999)	Mailed questionnaire	Non-profit
11	Observational follow-up of the Trials of Hypertension Prevention (TOHP I and II)	Follow-up started in 2000 and ended in 2004	Gap (1990 to 2000) for TOHP I and gap (1995 to 200) for TOHP II	Central follow-up conducted by mail and phone	Government

	Post-trial follow-up study	Duration of post-trial follow-up	Timing of trial and post-trial follow-up	Method of data collection	Primary funding source type
12	Multicenter Study of Hydroxyurea in adult sickle cell anemia (MSH)	5 additional years occurring 1996 to 2001	Continuous	Visits annually to collect medical history; medical records	Government
13	Medical and surgical therapies for gastroesophageal reflux disease (GERD)	10.6 years after randomization starting 1997 to 1999	Gap (1988 to 1997)	Visits (exam, pH monitoring, questionnaires); death from autopsy results, hospital records, and death certificates	Government
14	Long chain polysaturated fatty acid supplementation in infant formula and blood pressure	Cohort of 6 year olds followed in 1998 to 2000	Gap (1992 to 1998)	Clinic visit (blood pressure, demographic and clinical questionnaire, psychological assessments)	Industry
15	Diabetes Prevention Program Outcomes Study Continued Follow-up	5.7 additional years with continued treatment and intervention starting 2002 to 2008	Gap (2001 to 2002)	Clinic visit (exam, glucose values, weight loss, blood pressure, lipids)	Government
16	Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) extended follow-up	2 years of additional with continued pravastatin treatment	Continuous	Clinic visits (exam, cholesterol, adverse events)	Industry

Table 3**Recommendations for making extended follow-up of trials more feasible**

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1	Recognize that the desire of investigators to transition to follow-up usually does not emerge until the trial is near the end or after it has ended and design and plan for the possibility. If there is to be a seamless transition to follow-up, funding for follow-up has to be secured when the trial winds down. For that to happen, funding applications have to be submitted in time for completion of the review, award, and possible re-submission and re-review periods to be completed before funding for the trial ends.
2	Help established clinical centers maintain the study infrastructure as long after close of the trial as possible. Once the infrastructure is gone, the chance of any form of active follow-up markedly diminishes.
3	Ask study clinics to maintain IRB or ethics approvals after the close of the trial. Follow-up involving contact will likely require new consents. It is less labor intensive to obtain approvals for follow-up if submitted as amendments to existing approvals than it is to prepare new proposals. However, some IRBs charge a fee for reviewing yearly renewals; if funding lapses, continuing IRB approvals at all clinics may not be possible.
4	Inform study participants, on departure from trials, that they may be contacted later and locator information should be updated on departure; this is prudent even if there is no plan to transition to follow-up when people depart.
5	Commission the coordinating center to assemble a central file of names, addresses, and other locator information for persons in the trial on close of the trial. Obtain IRB approval and participant consent for such collection early in the course of the trial. The ability to re-contact is important in any trial where there is possibility of late term treatment effects. Even mortality follow-up, such as in the Coronary Drug Project or Multiple Risk Factor Intervention Trial, is precluded once clinics are closed without a central file of names and addresses.
6	Design data collection schedules and forms or screens in the follow-up study with merging the trial and follow-up data in mind. Minimize differences in the data collection methodology
7	Minimize the time between the trial and follow-up study. The number of people who can be contacted and who are willing to resume follow-up after from the end of the trial will diminish as the time between contacts increases.
8	Continue to attempt to contact participants who might have previously been too busy or uninterested in continued participation in the trial or earlier stages of the follow-up study (unless the participant explicitly said not to contact him/her again). In trials of children or in trials of participants who are also going through a transition phase in their life, interest in participation will likely wax or wane with time.
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