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Memorandum

To: Trialists

Fr: Curt Meinert

Re: On the morphing of trials to followup studies

A morphed trial is one that has changed form. The morphing can be during the trial (eg, by changing the dosage schedule for a treatment or by adding or subtracting a treatment) or can be after the trial is finished by transformation to observational followup. The followup may be without any person contact (eg, as the case with mortality followup via death indices) or via direct person contact. The contact may involve being seen at study clinics, may be by telephone or letter, or combinations thereof.

Examples of in-house trials that have morphed to followup are:

Studies of Ocular Complications of AIDS (SOCA)
-cum-
Longitudinal Studies of Ocular Complications of AIDS (LSOCA)

Childhood Asthma Management Program (CAMP)
-cum-
Childhood Asthma Management Program Continuation Study (CAMPCS)

Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)
-cum-
Alzheimer's Disease Anti-inflammatory Prevention Trial-Followup Study (ADAPT-FS)

The Multicenter Uveitis Steroid Treatment Trial (MUST Trial or MUSTT) has a funding proposal pending for morphing to followup.

The contacts in LSOCA and CAMP, and those planned in MUSTT, are via regularly scheduled followup clinic visits. Contacts in ADAPT are by telephone with clinic visits only if needed for diagnoses of dementia. LSOCA, CAMP, and MUSTT are multiple contact designs. ADAPT is a one or two contact design.

The transition was seamless for LSOCA and CAMPCS and may be for MUSTT, if a pending funding application is funded. In ADAPT-cum-ADAPT-FS transition was not. There was a two year dark period before transition.

Morphing to followup happens because of investigator interest in the long-term effects of treatment and in the natural history of the disease or heath condition represented in the trial. The followup may involve direct contact (as the case in the morphs listed above) or no contact

at all in mortality followup (eg, as in the Coronary Drug Project (CDP) and the Multiple Risk Factor Intervention Trial (MRFIT); Canner et al; Fifteen year mortality in Coronary Drug Projects patients: Long-term benefit with niacin; J Am Coll Cardiol 1986; 8:1,245-55 and Eberly et al; Multiple-stage screening and mortality in the Multiple Risk Factor Intervention Trial; Clin Trials 2004; 1:148-161).

There is no yellow brick road from trials to followup. Planning is difficult because the possibility of morphing to followup typically does arise until the trial ends. Hence, the best one can do is to provide a list of suggestions apropos to morphing.

Suggestion 1: Recognize that the desire of investigators to transit to followup usually does not emerge until the trial is near the end.

Comment: If there is to be any hope of seamless transition, funding for followup has to be in hand when the trial winds down. To have any chance of that happening, funding applications have to be submitted in relation to close out. The need for funding makes seamless transition white knuckle affairs. CAMP is presently in a white knuckle period as investigators wait to see if their second attempt at funding for a fourth round of followup visits succeeds. MUSTT is awaiting word on its funding proposal for followup.

Suggestion 2: Recognize that any trial can morph, but for followup to be useful it has to be possible to follow the majority of people enrolled in the trial and there has to be compelling rationale for followup.

Suggestion 3: Recognize that the productivity of the research group may be markedly enhanced by morphing to followup.

Comment: Consider SOCA and CAMP and its publication record pre and post morphing. Counting publications through one year after the start of funding for followup as pre-morph publications (2000 and 2001 for SOCA and CAMP, respectively) and after that date as post-morph publications yields 17 and 14 pre-morph publications for SOCA and CAMP, respectively, and 31 and 109 post-morph publications for SOCA and CAMP, respectively.

Suggestion 4: Maintain the study infrastructure as long after close of the trial as possible.

Comment: Once the infrastructure is gone, the chance of contact followup markedly diminishes.

Suggestion 5: Instruct study clinics to maintain IRB approvals after the close of the trial.

Comment: Followup involving contact will require new consents (unless covered in original consents; unlikely). It is far less labor intensive to obtain approvals for followup if submitted as amendments to existing approvals than it is to have to prepare new proposals.

Suggestion 6: If the trial is masked, consider keeping the mask in place for study subjects if there is a plan to morph to followup; a particularly important consideration if the primary motivation for followup is to assess late effects of treatment.

Comment: The wisdom of keeping the mask in place depends on what study subjects need to know about their treatment on departure from the trial. If people need to know treatment for continued care, the option of retaining the mask is not reasonable.

Suggestion 7: Study subjects, on departure from trials, should be informed of the fact that they may be contacted later on; prudent even if there is no plan to morph to followup when people depart.

Comment: Obviously people who say they do not wish to be contacted should not be recontracted.

Suggestion 8: Update locator information for study subjects as they depart the trial.
Comment: A prudent practice regardless of whether there are morphing plans.

Suggestion 9: In multicenter trials, 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. Inform study subjects of the file and reasons for it.
Comment: The ability to recontact is important in any trial where there is possibility of late term treatment effects. Mortality followup, such as in the Coronary Drug Project (CDP) or the Multiple Risk Factor Intervention Trial (MRFIT), is precluded once clinics are closed without a central file of names and addresses.

Coordinating centers vary as to practice of having names and addresses of persons studied in their databases. The worry of IRBs with coordinating centers that have names is breaches of confidentiality. Hence, an increasingly common practice is for coordinating centers to forego collection of personal identifiers. This means that the only route of contact with study subjects is via study clinics where persons are seen. Even when the trial is ongoing the absence of an identifier file in the coordinating center is problematic. For example, that absence meant that the coordinating center in ADAPT could not help clinics prepare mailings to study subjects on close of ADAPT to inform them of the treatment they were on. Likewise, mortality sweeps at the end of the trial using the National Death Index or Social Security Administration death file has to be done by clinics. Once the trial is finished and the investigator group has disbanded there is no viable means for mortality followup without a central file of names and addresses.

Note: The ability to assemble that file will depend on what is in IRB approvals for clinics and coordinating centers. Creation of the file will be difficult if consent forms contain statements specifically indicating that subjects' names and addresses will not be transmitted to the coordinating center.

Suggestion 10: Recognize that merging data from the trial and followup will create "denominator" problems for calculating incidence rates for events when combining data for the trial and followup study.

Suggestion 11: Collect baseline data anew for people enrolled for followup.
Comment: There will be need to characterize differences in people enrolled in the trial and in the followup study and there will be need for new baseline data for changes observed during followup.

Suggestion 12: Minimize difference in baseline data collection.
Comment: Minor wording changes in data items common to the trial and followup makes comparison across the two components of study problematic.

Suggestion 13: Keep in mind that the method of close out influences morphing.
Comment: Common closing date designs are logistically more amenable to transitions to observational followup than anniversary close out designs.

Suggestion 14: The number of people who can be contacted and who are willing to resume followup after separation from the trial will diminish as the period of darkness before contact increases.
