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Achieving Milestones as a Pre-Requisite for Proceeding with a Clinical Trial

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Abstract

INTRODUCTION—While the National Institutes of Health (NIH) invest 30 billion dollars in research annually, many funded studies fail to generate results that can inform practice. The NIH introduced a phased funding mechanism as one potential solution. Study-specific milestones are established for an initial pilot phase. We assess the utility of this phased approach through the ongoing Electroencephalography (EEG) Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) pragmatic clinical trial. The hypothesis of the trial is that EEG guidance of general anesthesia, through prevention of EEG suppression, can decrease postoperative delirium and its downstream negative sequelae.

METHODS—In collaboration with study stakeholders, we identified critical milestones for the ENGAGES study, with themes common to many clinical trials. These themes include (1) regulatory tasks; (2) enrollment targets; (3) feasibility and impact of study intervention; (4) primary outcome incidence; (5) measurement reliability of primary outcome; and (6) follow-up. Progress in achieving the milestones was assessed at regular intervals during the pilot phase by

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ENGAGES investigators, the National Institute on Aging (NIA) program officer, and a non-partisan research organization (Westat).

RESULTS AND MAJOR FINDINGS—Regulatory tasks, including IRB approval, infrastructure establishment, and trial registration were completed on schedule. (1) A total of 117 patients were randomized, exceeding the target by 51. (2) The EEG-guided protocol was successfully implemented, and a relevant effect on anesthetic practice was demonstrated (decrease in median age adjusted minimum alveolar anesthetic concentration (MAC) from 0.93 to 0.78 [$p<0.001$] and increase in median proportion of zero EEG suppression time from 87% to 94% [$p<0.01$]). (3) Nearly all patients (115/117, 98.3%) were assessed for delirium using the Confusion Assessment Method (CAM), and (4) the delirium incidence was similar (28.1%; 95% CI, 20% to 37%) to the estimate (25%) used for the sample size calculation. (5) Good inter-rater reliability of delirium assessment was demonstrated (kappa= 0.94 [95% CI, 0.86 to 1]). Finally (6), one-month follow up vital status data were obtained for 96.9% of patients with 85.7% of patients completing at least 1 survey.

CONCLUSION—With the ENGAGES trial, we demonstrated that key milestones can be identified and progressively assessed during a pilot phase. Success in attaining appropriate milestones hypothetically predicts meaningful completion of a study, and can provide justification for proceeding beyond a pilot phase. The impact of this phased approach on return on investment and scientific yield requires additional study.

INTRODUCTION

Randomized clinical trials have impacted healthcare delivery around the world,¹ and provide a foundation for determining the effectiveness of new therapies and innovations.² However, large clinical trials are expensive. The National Institute of Health (NIH) invests 30.1 billion dollars in medical research annually and it is important that such investments translate into scientific discovery and impact health outcomes. Unfortunately, many funded trials do not yield benefits for healthcare or sufficiently advance science. A recent study of 244 cardiovascular interventional trials funded through the National Heart, Lung and Blood Institute between January 1, 2000 and December 1, 2011 found that fewer than two-thirds of these funded studies published data within 30 months of completion.³ Additionally, many studies are not completed due to infeasibility or futility.⁴ Many studies have poor study design, are too complex or are not powered to answer the hypothesis in question. Others yield results which are not translatable to a clinical setting.

As a part of continuing efforts to increase the yield of research investments, the NIH recently introduced a phased funding mechanism for clinical trials incorporating two distinct periods, the UH2 and UH3.⁵ During an initial one-year pilot phase (UH2), investigators are required to reach essential trial milestones. Milestones are selected in collaboration with study stakeholders, including the funding agency, and are designed to address potential barriers that may impede successful study launch, timely trial completion, and the generation of useful scientific results. Attainment of these milestones serves as partial justification for allocating funding for the subsequent, lengthier UH3 phase within which the full trial is carried out. Conversely, failing to meet critical milestones during the UH2 phase signifies residual barriers that must be overcome for successful study conduct. Alternative research

plans may be necessary and, if barriers cannot be overcome, funding may be best directed towards other potential trials. In total, employing this phased mechanism may divert funding to larger numbers of promising pilot studies, while long-term funding is focused on those studies demonstrating a high likelihood of timely completion with the generation of meaningful scientific results.

Investigators at Washington University received funding through the UH2/UH3 mechanism from the National Institute on Aging (NIA) to conduct the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study (NCT02241655).⁶ The ENGAGES study is a pragmatic, randomized controlled trial testing whether electroencephalography (EEG) guidance of general anesthesia can decrease postoperative delirium, a common neurological complication of surgery in older adults, and its downstream negative sequelae. The motivation for this pilot was to demonstrate that the prospectively identified critical study milestones could be met, justifying the pursuit of a larger, pragmatic clinical trial. In this manuscript, we present the methods for determining milestones for the pilot phase of the ENGAGES trial, report successes and failures in reaching milestone goals, and demonstrate how the process provided confidence in and facilitated funding of the expanded four-year UH3 study phase.

METHODS

The ENGAGES trial was one of six studies funded through the UH2/UH3 mechanism. The study was approved by Washington University Institutional Review Board (IRB) and written informed consent was obtained from all subjects. The NIH appointed an independent research consulting corporation (Westat, Rockville, MD) to evaluate progress during the UH2 period for all six individual trials. Investigators from each research team participated in monthly conference calls with Westat and a NIA program official. The agenda of these regular meetings centered on identification of study tasks and barriers, establishing related milestones, and assessment of milestone progress. Milestones served both as a report card for demonstrating candidacy for the next phase and as an unambiguous shared action plan for carrying out a successful pilot study.

Barriers to the launch and conduct of clinical studies often fall within typical themes. The overall trial design, detailed study protocol, and other logistical considerations of the ENGAGES study were examined for such barriers. Those most likely to delay launch, prevent timely completion, or compromise the scientific validity of the ENGAGES study were incorporated into milestones (Figure 1). Common thematic categories for these barriers across studies and the corresponding ENGAGES milestones are described as follows (Table 1):

- 1. Standardization, Transparency, and Clearances:** Sound research practice requires adherence to investigative conventions.⁷ Several considerations must be addressed to minimize bias, control undesired variation, promote transparency,⁸ and facilitate reproducibility.⁹

A study protocol and manual of procedures should be prepared, including case report forms (CRF), data collection source documents and processes,

standardized definitions, and delegations of trial conduct responsibility. Other regulatory documents may be required depending on trial features (e.g., FDA form 1572 for new investigational drug studies). Trial endpoints and data analysis plans should be prespecified.¹⁰

The trial should be registered in the scientific community, for example at *clinicaltrials.gov*, with inclusion of the aforementioned elements to promote transparency of methods, protocol adherence, sound analysis practices, and shared scientific knowledge.¹¹ To promote the highest level of transparency and knowledge sharing, the study protocol should be published or otherwise disseminated early in the launch process, even for observational studies.¹²

Specific clearances are needed before study launch to promote patient welfare. These include approval from an institutional review board, institutional clearances and depending on the nature of the study, additional authorities may need to provide approval, such as an investigational pharmacy or a radiology committee.

The prompt shared recognition of necessary pre-study documents and clearances helps to facilitate research team communication and avoid delays. In particular, the ENGAGES study team identified preparation of the detailed study protocol, finalization of data collection tools, public registration of the study, and obtaining IRB approval as key barriers within this domain.

2. **Recruitment:** The ability to enroll a sufficient number of eligible patients over a projected time interval is a common barrier to study conduct. The recruitment start date, recruitment completion date, and requisite average rate of subject recruitment should be plainly identified. Studies often launch with an attenuated recruitment rate to optimize successful study conduct, but the early phases of a study must also be leveraged to determine whether the recruitment rate necessary for the full trial is realistically achievable¹³. Additionally, since clinical trial drop-out rates can be as high as 30%¹⁴, attrition of patients between recruitment and the completion of outcome assessments should be evaluated. If recruitment is inadequate or outcome collection is compromised, contributing etiologies must be identified and addressed.

For the post-pilot phase of the ENGAGES study, a sustained randomization rate of at least 32 patients per month would be needed to complete the trial within the funding period. To permit early familiarization of the research team and clinical staff to study processes, an approximate 50% recruitment rate of 12–16 patients randomized per month (66 total patients during the six-month pilot study period) was selected as the recruitment milestone for the pilot period. For the later pilot period, it was collectively recognized that surpassing this milestone and approaching the necessary long-term rate of 32 patients per month would further allay any concerns regarding the long-term feasibility of trial recruitment.

3. **Study Intervention:** In clinical research, and particularly in large and pragmatic clinical trials, the application of study treatments may depend on factors such as

clinical personnel with diverse beliefs, expertise, and usual practices. Such diversity is likely to introduce variation that must be recognized, and if appropriate, mitigated. Trials designed with an explanatory approach generally aim to deliver intervention and control treatments with high fidelity so that the intervention's effect can be accurately assessed.¹⁵ In contrast, pragmatic studies attempt to study the application of treatments in real world settings that are accompanied by greater variation in delivery.¹⁵ Still, overlooking practical standardization methods in pragmatic studies, such as providing basic education to clinicians about treatment protocols, may compromise trial results. Beyond the importance of ensuring high fidelity treatment application for generating useful results within the study, detailed descriptions of any standardized methods for treatment delivery are critical for replication in subsequent studies or application to clinical medicine.

Any study presents unique barriers to high fidelity delivery of trial interventions. Considerable foresight is required to anticipate and overcome these barriers. Advance consideration must be given to sources of treatment variation. Measures to manage undesired treatment variation may be introduced¹⁶ depending on the study design and trial objectives.¹⁷ Action plans may include training of clinicians applying treatments, provision of reference materials, checklists, adherence reminders, quality assurance monitoring, and summative adherence reporting. In addition to the introduction of prospective measures, intervention fidelity should be monitored throughout the trial so that undesired sources of variance can be promptly identified and mitigated as they appear.¹⁶ Such measures should be considered and applied in accordance with the general design of the trial. For example, for a largely explanatory trial more aggressive measures would be implemented whereas for a pragmatic trial less behavioral modification would be pursued.

For the ENGAGES study, anesthesiology clinicians are tasked with dosing anesthesia using a novel EEG-guided protocol versus routine anesthetic care. Using input from study stakeholders, a plan for expeditious and reproducible training of diverse anesthesiology clinicians on intra-operative EEG interpretation was devised. Practical methods for promoting knowledge retention were also selected. Specific methods were prioritized because they would be feasible to replicate within future studies or clinical care. Many anesthesiology clinicians were trained in EEG waveform interpretation and the EEG-guided anesthesia protocol through a focused lecture. The training session employed a skills test to assess efficacy. These components were then embedded in a computer-based module for ongoing use. Additional web-based instruction (www.icetap.org) and paper-based teaching materials were prepared to promote maintenance of knowledge. Quick reference cards were prepared that could be easily used during the course of clinical care. Additionally, prior to each ENGAGES operative case, an email was sent to the anesthesiology clinicians with a short reminder including the principals of treatment group assignment, a brief reference guide, and links to refresher materials. Research team members

were made available in the perioperative period to answer additional questions regarding the EEG-guided anesthetic protocol. For each research patient, anesthesiology clinicians were asked to complete an adherence checklist assessing whether they had adhered to treatment group principals, whether any barriers had impeded carrying out the assigned treatment, and whether any complications had occurred during the surgical procedure that could be related to the assigned treatment. Additionally, to assess the treatment group fidelity, differences in volatile anesthetic concentrations and EEG suppression were assessed between the treatment and control groups in the pilot cohort (i.e., age-adjusted fraction of minimum alveolar anesthetic concentration [MAC] and elapsed time with a suppressed EEG waveform). These educational tasks and assessment measures were encapsulated in pilot phase milestones.

4. **Outcome and data collection:** Accurate, reliable, and maximally complete collection of outcome data is necessary for a scientifically useful trial. As outcome data may be subject to laboratory instrument, research personnel, or patient report variation, proactive efforts to promote precise data collection are important. It is additionally important to institute up-front strategies for minimizing missing outcome data and the loss of patients to follow-up. The mechanisms for complete and accurate data collection should be clearly defined and demonstrated before study launch. Customized CRFs and electronic databases must be created to standardize data collection.¹⁸ Thresholds for the acceptability of missing study data should be determined, recognizing the feasibility of collecting specific study measures. Establishment of transparent milestones and a monitoring plan for missing data allows the research team to recognize gaps in data collection, enabling early adjustments in data collection procedures.

In the ENGAGES study, the primary outcome of delirium is determined using the Confusion Assessment Method (CAM) tool, an assessment modality that requires training. To ensure that study staff was able to accurately obtain the primary outcome measure, a comprehensive training program on the CAM tool was defined and instituted for research personnel. Thereafter, investigators measured both inter-rater agreement and test-retest reliability for CAM assessments carried out by the research team. Additionally, since delirium has acute onset and often fluctuates, it was deemed important to assess patients for delirium daily for five postoperative days in order to maximize the detection of incident postoperative delirium. Finally, the ability to reliably collect 30-day secondary outcomes data from discharged post-operative patients was identified as a potential barrier. These aspects of trial conduct were assessed in the UH2 milestones.

5. **Patient Safety:** Patient safety is the primary consideration when conducting any clinical trial. The establishment of a Data Safety Monitoring Board (DSMB) before study launch is essential. A DSMB charter must be prepared and approved, defining the responsibilities of the DSMB and procedures for reviewing safety data. The investigator and DSMB must together ensure that the

required safety data are being collected and reviewed in a timely fashion through construction of a pre-specified DSMB plan.¹⁹ Thoughtful communication amongst the DSMB members and investigators prior to study launch is essential to ascertain potential risks, ensure that safety data are reliably collected, construct plans for review of safety data, and establish a protocol for responding to safety data. These considerations were incorporated in the UH2 milestones.

A comprehensive list of critical milestones relating to the above categorization of study tasks and barriers were collaboratively selected by the investigative team, the funding stakeholder (the NIA), and the independent consulting organization (Westat) (see Table 1).

RESULTS

At the end of the UH2 phase of the ENGAGES trial, investigators were successful in completing the predefined study specific milestones and were subsequently awarded additional funding for the UH3 phase. The outcomes of milestones selected for the pilot phase of the UH2 phase of the ENGAGES trial were as follows (Table 1):

1. Standardization, Transparency, and Clearances

The study protocol, detailed study manual of operations, and data collection forms were completed by the target dates. IRB approval of the study (August 2014) and the necessary regulatory documents were completed prior to recruitment in the trial which began in January 2015. To facilitate transparency, the trial was registered on *clinicaltrials.gov* in December 2014 and the study protocol was submitted for publication in a peer-reviewed journal.⁶

2. Recruitment

Over the 25-week UH2 pilot period, 117 patients were randomized, producing an overall recruitment rate of 19.5 patients per month. An additional 30 patients were enrolled but did not proceed to surgery. This exceeded the randomization goal of 66 patients (10–14 patients per month). Figure 2 illustrates the randomization milestone for the pilot study, the randomization rate that would be needed for the expanded (post-pilot) study phase, and the actual randomization rate that was observed during the UH2 phase. In the later pilot period, a comparative analysis of the ongoing recruitment rate and future recruitment goal of 32 patients per month was carried out. Research team resources and additional subjects were identified that would enable the higher recruitment rate to be achieved during the UH3 phase.

3. Study Intervention

Several initiatives were carried out to promote and assess the fidelity of the study treatments including developing training modules, deploying checklists, and assessing physiologic data from the pilot study subjects. Aggregate data from the 117 patients randomized in the UH2 phase showed (1) a reduction in volatile anesthetic concentration in the EEG-guided treatment group relative to the control group (median age-adjusted MAC, 0.78 versus 0.93

respectively; $p < 0.001$), (2) a reduction in EEG suppression in the EEG-guided group (median proportion of time with zero EEG suppression, 94.0% versus 87.0%; $p = 0.008$), (3) and higher median bispectral index values in the EEG-guided group (45.5 versus 42.0; $p = 0.002$). Thus, the aggregate pilot data supported that the EEG-guided protocol resulted in anesthetic administration alterations, and these were associated with attendant decreases in EEG suppression.

4. Outcomes and data collection

The 38 concurrent inter-rater delirium assessments demonstrated almost perfect agreement (Kappa = 0.94 [95% CI, 0.86 to 1]). The strong inter-rater agreement indicates excellent psychometric properties of the CAM tool as employed by the research team following the training program. Test-retest reliability of 35 assessments was carried out by two separate assessors interviewing the same patient approximately two hours apart. This revealed a kappa statistic of 0.53 (95% CI, 0.24 to 0.83), indicating moderate agreement. The moderate test-retest agreement obtained over time in individual patients is unsurprising, given the fluctuating nature of delirium.

Once pilot enrollment commenced, key aggregate outcomes were assessed to ensure that outcomes data would be complete and enable valid results. Within the 117 patients randomized during the pilot period, CAM assessments were successfully carried out on 98.3% of patients and revealed a delirium incidence of 28.1%. This is consistent with rates estimated from the literature,²⁰ which were used in the trial sample size power calculations. Ninety-eight patients were eligible to be contacted for 30-day follow up during the UH2 phase, and multiple methods were used to ensure high follow-up rates including phone calls, emails, letters, and contacting family members. A total of 84 patients (85.7%) completed at least one survey approximately 30 days following surgery, 3 declined, 2 patients died, and 9 patients did not respond. For the 9 non-responders, the 30-day vital status (whether alive or dead) was obtained for 6 patients. This exceeded our pre-specified goal of >85% follow up rate at 30 days.

5. Patient Safety

The DSMB was established on time for study launch and the DSMB charter and safety assessment plans were approved. As outlined in the safety monitoring plan, all adverse events that occurred within 30 days of the study intervention were initially reviewed by study investigators to determine whether they were possibly related to the trial intervention. Based on the recommendation of the DSMB, the ENGAGES team also hired an unbiased safety officer to review any serious adverse events to determine relatedness to the study. Based on aggregated data from the pilot study, the safety officer, DSMB board, and ENGAGES investigators all concluded there was no evidence of study-related harm to ENGAGES participants.

Discussion

This manuscript provides general guidelines for rigorous conduct of large clinical trials, and specifically highlights the utility of adopting a phased approach incorporating trial-specific

milestones. The milestones important to the long-term success of the ENGAGES trial were identified, tracked, and achieved during a pilot funding year (UH2) using the novel phased funding mechanism (UH2/UH3) introduced by the NIH. The execution of important UH2 phase milestones demonstrated the feasibility of the study during the pilot year and provided motivation for the ongoing funding of the multi-year study phase (UH3) of the trial. Challenges typically encountered with study implementation were assessed for those that would be most informative to the success of the ENGAGES study. By ensuring the milestone selection process was collaborative, all stakeholders had a voice in ensuring that the aspects of the study they felt were most at risk for impeding success would be carefully tracked. Therefore, when all the selected milestones were successfully achieved during the initial year of funding, stakeholders were reassured that the study was feasible and was expected to generate useful scientific findings in a timely fashion. The ENGAGES study is currently in the midst of its 4-year expanded UH3 funding phase with an expected trial completion date of June 2019. Several of the UH2 phase milestone measures, such as recruitment rate tracking and treatment fidelity monitoring, have been implemented into continued monitoring during the long-term UH3 study phase.

Widespread application of milestone processes into large, multi-year trials may promote higher rates of trial completion, earlier dissemination of knowledge, and fewer trials that do not produce scientifically useful results. Failures in these areas may occur for several reasons. For example, in large pragmatic trials such as the ENGAGES study critical problems may include: (1) statistical planning that does not reflect actual primary outcome incidences in the study population; (2) inadequate research infrastructure to reliably collect study data; (3) insufficient ongoing enrollment to meet study objectives in a timely fashion; (4) failure to implement methods for ensuring reliable administration of study treatments; and (5) failure to complete regulatory or define study processes on time for an expeditious study launch. Collaborative consideration by study stakeholders such as patient representatives, clinicians, and researchers may be able to anticipate the majority of these potential barriers in advance. Early recognition allows for shared problem-solving and may enable identification of flaws in study design. When major obstacles or limitations are identified, the study should either be adapted or abandoned to avoid further wasted investments by patients, researchers, clinicians, and funding agencies. Conversely, there is a potential concern that the milestone process could increase waste because studies that are likely to succeed might be unnecessarily terminated at the end of the pilot phase. Therefore, it is essential even when all milestones are not accomplished, to assess the risks and benefits of continuing the study, and to consider if barriers might be surmountable.

Despite the apparent successful application of the UH2/UH3 milestone-based phased funding approach in the ENGAGES trial described here, the approach has several potential limitations that must be clarified by further study. First, the utility of the milestone process is likely heavily dependent on accurate identification of critical milestones early in the study process. While some metrics (e.g., adequate rates of subject enrollment) are applicable across all studies, individual studies face unique challenges in most other aspects of their design and launch. Failure to successfully identify even one critical challenge early in the study may compromise the utility of the entire milestone approach. We believe the

involvement of a broad coalition of study stakeholders may help to circumvent such a problem.

The role of the milestone process in identifying or mediating successful trials requires additional study. In the ENGAGES trial, the use of the UH2 milestone process was associated with expeditious study launch, successful continued funding, the overcoming of key study barriers, and continued successful study conduct in the early UH3 study phase. However, to what extent the milestone process mediated these early successes is not known. Additionally, the impact of the milestone process on late study metrics must be clarified. These include timely study completion, generation of useful scientific data, rapid dissemination of results, and applicability of study interventions to real world care. It remains possible that the short-term metrics reported in this current study may not be sufficiently associated with success in the more important long-term metrics. Additionally it remains possible that previously unrecognized pitfalls might arise later during the study period and compromise study conduct.

Importantly, a companion trial has been launched in Canada (ENGAGES-Canada, NCT02692300). ENGAGES-Canada investigators have similarly created their own study specific milestones in order to further evaluate success at the pilot phase and to inform whether or not to proceed with a larger trial. Although many milestones may be similar to those described in this manuscript, it is envisaged that Canadian conditions and stakeholders will identify some different challenges to the trial's conduct.

In summary, during the pilot of the ENGAGES study, the UH2/UH3 milestone-based phased-funding process was associated with successful navigation of early trial barriers and competition for continued funding. Additionally, all study barriers that became apparent by the completion of the pilot period were anticipated through early collaborative discussions amongst study stakeholders. The long-term utility of study milestone processes requires further research. If the utility of such processes is demonstrated across trials, such an approach could become an invaluable tool for reducing wasted resources and promoting high yield from trial investments on the part of patients, funding institutions, clinicians, and researchers.

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Key Points

Question

Can the identification and tracking of key study milestones early in a clinical trial be used to promote the study's success and demonstrate its feasibility?

Findings

Investigators at Washington University were able to select and meet key early study milestones, which suggested long-term feasibility and the potential for significant scientific impact.

Meaning

The careful selection and pursuit of key study milestones early in a clinical trial may drive success in study conduct and help to justify continuing the study.

Figure 1. CONSORT diagram for the ENGAGES study, indicating the key milestones for the pilot phase. (AE, adverse event; SAE, serious adverse event.)

Figure 2.
Randomization rates during the UH2 phase and Projections for the UH3 phase

Table 1

Common thematic categories for study tasks and barriers, corresponding milestones selected for the ENGAGES study, and milestone outcomes for the ENGAGES study

	I. Milestone Categories	II. Typical Tasks and Barriers	III. Milestones Selected for UH2 Phase of the ENGAGES Trial	IV. Outcomes of ENGAGES Milestones
1	Standardization, Transparency, and Clearances	Study Protocol and Manual of Operations; Institutional Review Board approval; data collection instruments	Complete logistical tasks to allow study launch by January of funding year including: Study protocol, manual of operations, clinicaltrials.gov registration, data collection tools finalized, IRB approval obtained	IRB approval obtained (8/2014), Study Protocol and Manual of Operations completed (1/2015), and other regulatory documents finalized. Pilot study launched on schedule (1/2015).
2	Recruitment	Establish feasibility of recruiting, enrolling, and collecting data on the proposed number of eligible patients within the study's funded timeline	Enroll patients at more than 50% the rate that would be required for the expanded phase (66 patients over 6 months)	147 patients were consented and 117 randomized (exceeding the target of 66 and nearing the rate required for expanded phase enrollment)
3	Study Intervention	Implement appropriate measures to ensure reliable administration of intervention and control treatments	Complete a training program for anesthesiology clinicians on EEG-guided anesthetic management Establish treatment arm fidelity by assessing whether EEG-guided patients are administered less anesthetic and demonstrate reduced EEG suppression compared to standard care patients	Initially 55 clinicians were trained on the EEG protocol with continuous ongoing training during the UH2 phase. The treatment group showed lower median age-adjusted MAC (0.78 versus 0.93 MAC; $p<0.001$), higher median proportion of time with zero EEG suppression (93.0% versus 78.0%, $p=0.01$), and higher median bispectral index values (45.5 versus 42.0; $p=0.002$)
4	Outcomes and Data Collection	Establish reliable means for collecting valid outcome and other data. Show that outcome rates in study population are consistent with power calculations	Train research staff on delirium assessment methods and establish reliability ratings for delirium assessments Affirm adequate incidence of primary outcome in overall study population (25% used in power calculations) Obtain 30-day follow-up data on >85% of enrolled patients	Training completed; 38 concurrent inter-rater delirium assessments demonstrated almost perfect agreement (Kappa = 0.94 [95% CI, 0.86 to 1]) Delirium incidence 28.1% (95% confidence interval, 21.0% to 42.0%). Follow up data were obtained on 86.0% of eligible patients.
5	Patient Safety	Establish mechanisms for collecting safety data; prepare safety data plan in collaboration with DSMB; review safety data for evidence of harm (or exceptional clinical benefit in some studies)	Complete review of safety data by research team and DSMB charter; Use safety plan in collaboration with DSMB to assess for evidence of harm	AE/SAE collection and reporting system established. The research team and DSMB convened and reviewed AE/SAE's reported during the pilot phase and agreed there was no suggestion of patient harm related to the conduct of the trial.