Pediatric Epilepsy
RESEARCH CONSORTIUM

The Aims Page

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The Aims Page is the **MOST IMPORTANT** part of a grant.

Call to arms and moral imperative
Advertisement and manifesto
Compelling and urgent
Concise and streamlined
The first thing you write, and the last thing you edit
It is the thing you think about in the shower

PERFECTION!!!!!!
DU NIT MISPEL WERDS!!!!!
THE GRAMMAR MUST BE AS BEST AS A TEXTBOOKS!!!

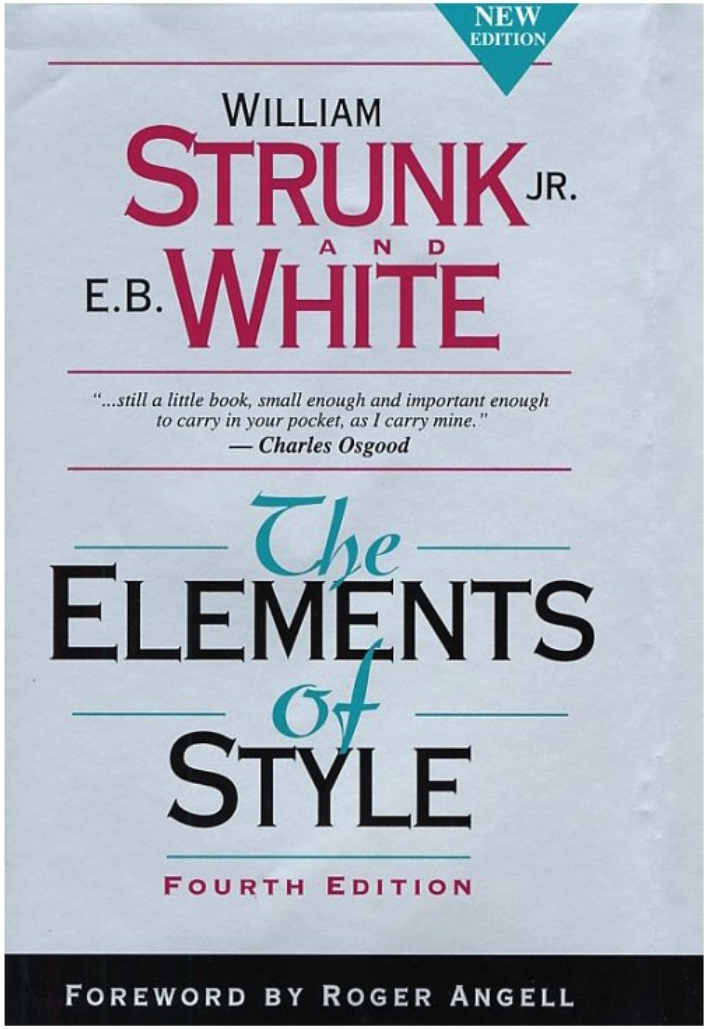
Read Strunk and White

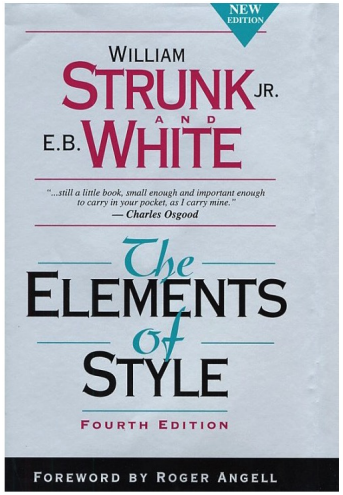
Elementary Principles of Composition

- RULE 14 – Use the Active Voice
- RULE 17 – Omit Needless Words

An Approach to Style

- RULE 4 – Write with nouns and verbs
- RULE 5 – Revise and rewrite
- RULE 16 – Be Clear



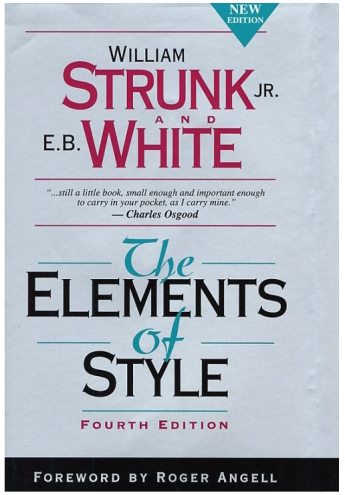


Vigorous writing is concise. A sentence should contain no unnecessary words, a paragraph no unnecessary sentences, for the same reason that a drawing should have no unnecessary lines and a machine no unnecessary parts. This requires not that the writer make all sentences short, or avoid all detail and treat subjects only in outline, but that every word tell.

16. Be clear.

Clarity is not the prize in writing, nor is it always the principal mark of a good style. There are occasions when obscurity serves a literary yearning, if not a literary purpose, and there are writers whose mien is more overcast than clear. But since writing is communication, clarity can only be a virtue. And although there is no substitute for merit in writing, clarity comes closest to being one. Even to a writer who is being intentionally obscure or wild of tongue we can say, "Be obscure clearly! Be wild of tongue in a way we can understand!" Even to writers of market letters, telling us (but not telling us) which securities are promising, we can say, "Be cagey plainly! Be elliptical in a straightforward fashion!" Clarity, clarity, clarity. When you become hopelessly mired in a sentence, it is best to start fresh; do not try to fight your way through against the terrible odds of syntax. Usually what is wrong is that the construction has become too involved at some point; the sentence needs to be broken apart and replaced by two or more shorter sentences.

Muddiness is not merely a disturber of prose, it is also a destroyer of life, of hope: death on the highway caused by a badly worded road sign, heartbreak among lovers caused by a misplaced phrase in a well-intentioned letter, anguish of a traveler expecting to be met at a railroad station and not being met because of a slipshod telegram. Think of the tragedies that are rooted in ambiguity, and be clear! When you say something, make sure you have said it. The chances of your having said it are only fair.



The POPI

- **P**roblem & Gap
- **O**pportunity & Idea
- **P**lan, Aims, Hypotheses
- **I**mpact

Problem
Gap

Problem
Gap

Opportunity

Idea
PLAN
Aims & Hypotheses

IMPACT

SPECIFIC AIMS

Introduction. Rare epilepsies are a devastating, heterogeneous group of diseases that begin in childhood. Affected individuals are a vulnerable and medically complex population with profound neurologic, medical, and psychiatric disabilities. There are reliable epidemiologic estimates for only a few of these diseases. Tuberous sclerosis (TS), for example, affects 1 neonate per 5700 live births.[1] However, for some diseases like Aicardi syndrome, estimates are limited to counts of known cases (900 in the US).[2] And for others, such as MERRF (Myoclonic Epilepsy with Ragged Red Fibers), there are no estimates at all.

Epilepsy is an ambulatory care sensitive condition -- high quality ambulatory care reduces emergency and inpatient care.[3-7] Thus variations in health services use can highlight insufficient ambulatory care. For example, frequent ED use[8-11] and a high ratio of ED to outpatient visits[12, 13] both indicate poor access to care and/or poorly controlled seizures. Given their medical complexity, individuals with rare epilepsies are especially reliant on high quality ambulatory care, yet risk factors of insufficient ambulatory care are understudied.

Several obstacles have impeded surveillance and epidemiology of the rare epilepsies. First, identifying individuals in large datasets is difficult. Although some diseases have specific billing codes (i.e. ICD-9 759.5 TS + 345.x epilepsy = TS with epilepsy), most are coded with nonspecific diagnoses like 345.9 (epilepsy unspecified) or 780.39 (other convulsions). Second, although caregivers have formed advocacy groups for individual rare epilepsies, these groups only recently united to support research. Third, many individuals seek care at multiple centers,[14-16] preventing a full assessment of their history at a single center.

There are new opportunities to study these diseases. First, broad use of electronic health records (EHRs)[17] now allows researchers to analyze large volumes of physician notes with text processing tools. A "regular expression", for example, is a robust, easy-to-share technique to specify a text search. Second, the Rare Epilepsy Network (REN)[18] has unified advocacy groups for rare epilepsies via a federally funded research consortium. Third, multi-institutional clinical data research networks such as the New York City Clinical Data Research Network (NYC-CDRN)[19] are gathering medical records from multiple institutions. New York City's wide income distribution[20] makes it an ideal location to study disparities in care.

Our central hypothesis is that text processing of clinical notes will improve surveillance and epidemiology of the rare epilepsies. We will use the NYC-CDRN to find affected individuals using EHRs from multiple centers. We will describe the incidence, prevalence, comorbidities, mortality, and insufficiency of ambulatory care for these individuals. Finally, we will develop, characterize, and disseminate a set of regular expressions that can find affected individuals via analysis of clinical notes.

Specific Aim 1: Assemble a cohort of individuals with rare epilepsies.
- ***Aim 1a.*** Collect clinician notes from people with suspected epilepsy at five centers, via the NYC-CDRN.
- ***Aim 1b.*** Catalogue synonyms for the rare epilepsies via (1) a survey of US Child Neurologists, (2) a survey of caregivers of affected individuals in the REN, and (3) a review of a sample of clinical notes.
- ***Aim 1c.*** Identify, classify, and validate cases of rare epilepsies, via a combination of clinician recall, site-specific registries, text search of notes, and chart review by experienced clinicians.

Specific Aim 2: Describe the incidence, prevalence, comorbidities, and mortality of rare epilepsies in Manhattan and Bronx, New York, via centralized chart review, using records collected from multiple medical centers, and linked to vital records. Examine the effect of socio-demographic factors on patterns of care.
- ***Hypothesis 2a.*** Incidence and prevalence of rare epilepsies are higher than currently described, particularly among individuals who are Black, Hispanic, or publicly insured.
- ***Hypothesis 2b.*** Comorbidity burden (medical complexity) increases the risk for death.
- ***Hypothesis 2c.*** Individuals who are Black, Hispanic, or publicly insured are more likely to use the ED frequently, and have a high ratio of ED to outpatient care.

Specific Aim 3: Develop an easy-to-disseminate set of "regular expressions" to identify individuals with rare epilepsies from clinical notes. Characterize the sensitivity, specificity, positive predictive value, and negative predictive value. Compare the set's performance to machine learning natural language processing algorithms.

Impact. Improved epidemiological estimates will guide clinical care, prioritize research initiatives, spur development of therapies by industry, and help caregivers understand these devastating diseases. The regular expressions will help centers identify individuals with rare epilepsies to support surveillance, research, quality improvement, care management, and referral to advocacy organizations. This work aligns with recent IOM recommendations[21] (1, 2, 4, 8, 9, 13) and with the 2014 NINDS Epilepsy Benchmarks (IC, IIC, IIF, and IVD).

PROBLEM & GAP What is the terrible thing you want to make better?

Audience: Your high school biology teacher

Length: 1 or 2 sentences

SPECIFIC AIMS

Introduction. Rare epilepsies are a devastating, heterogeneous group of diseases that begin in childhood. Affected individuals are a vulnerable and medically complex population with profound neurologic, medical, and psychiatric disabilities. There are reliable epidemiologic estimates for only a few of these diseases. Tuberous

Pitfalls

- Omitted
- Too narrow
- Too technical
- Not linked to human health or disease

PROBLEM & GAP What is the gap? What do know? What don't we know?

Audience: A neuroscientist you don't know

Length: 1-2 sentence to a few paragraphs

SPECIFIC AIMS

Introduction. Rare epilepsies are a devastating, heterogeneous group of diseases that begin in childhood. Affected individuals are a vulnerable and medically complex population with profound neurologic, medical, and psychiatric disabilities. There are reliable epidemiologic estimates for only a few of these diseases. Tuberous sclerosis (TS), for example, affects 1 neonate per 5700 live births.[1] However, for some diseases like Aicardi syndrome, estimates are limited to counts of known cases (900 in the US).[2] And for others, such as MERRF (Myoclonic Epilepsy with Ragged Red Fibers), there are no estimates at all.

LEV and PB are commonly used in current clinical practice,[4] yet there is uncertainty about their comparative effectiveness in infants.

(A longer example of the gap – three gaps described, one for each aim of the grant)

First, although a high dose regimen of ACTH has the best published response rates as first line treatment,[9-11] it is not clear how it compares to more recently developed regimens. For example, although a randomized controlled trial found low dose oral corticosteroids less effective than high dose ACTH,[9] there are now promising high dose oral corticosteroid regimens that have not been compared to high dose ACTH.[12]

Second, the outcome measures used across studies vary and often include subjective measures such as reduction in spasms, improvement in EEG, or parental report via telephone interviews. "Freedom from treatment failure," (i.e., no need for a second treatment, and no spasms at 3 months) is an epilepsy outcome that better aligns with the goals of physicians and families.[13]

Third, a major barrier preventing broader use of ACTH is its cost. Yet, superior efficacy may reduce long-term healthcare costs when the consequences of treatment failure are considered. A cost effectiveness analysis may help child neurologists negotiate improved access to ACTH for their patients.

Pitfalls

- “No one ever did this before” is not sufficiently compelling
- No explicit description of the gap
- Too technical
- Too much focus on literature review at the expense of a synthesis

OPPORTUNITY & IDEA. Why now?

Audience: A neuroscientist you don't know

Length: 1-2 sentence to a full paragraph

There are new opportunities to study these diseases. First, broad use of electronic health records (EHRs)[17] now allows researchers to analyze large volumes of physician notes with text processing tools. A "regular expression", for example, is a robust, easy-to-share technique to specify a text search. Second, the Rare Epilepsy Network (REN)[18] has unified advocacy groups for rare epilepsies via a federally funded research consortium. Third, multi-institutional clinical data research networks such as the New York City Clinical Data Research Network (NYC-CDRN)[19] are gathering medical records from multiple institutions. New York City's wide income distribution[20] makes it an ideal location to study disparities in care.

OPPORTUNITY & IDEA. *You* are part of the opportunity. Your data, your methods, your training, your track record.

Our prior work found that natural language processing can reliably identify risk factors for SUDEP in the electronic health record systems at five academic medical centers.

The UG3 phase will **leverage our existing infrastructure (Pediatric Epilepsy Learning Healthcare System[28] and an established, productive network of clinical researchers[1,4,29-49]**) to build an informatics pipeline to ensure: (a) timely identification, recruitment, and retention of participants; (b) secure, reliable, high-quality data collection from multiple sources; and (c) operational adaptability and efficiency.

OPPORTUNITY & IDEA. Alignment with the funder is also part of the opportunity

BACKGROUND, AIMS, and HYPOTHESES

Overview. There are cures for some children with severe pediatric epilepsy. However, these cures will always fail if the health system does not recognize affected children and deliver their cures. We propose to investigate how often cures are delivered to children with three types of severe pediatric epilepsy, using large national databases. This approach is the basic science of health services research, just as bench neuroscience is foundational for pharmaceutical and device development. The results will highlight gaps in our health system and guide innovations in pediatric epilepsy care. Our work fits squarely within CURE's mission to cure epilepsy, and thus transform and save lives.

OPPORTUNITY & IDEA. Central Hypothesis

Audience: A scientist you don't know

Length: 1 ***perfect*** sentence

Our central hypothesis is that text processing of clinical notes will improve surveillance and epidemiology of the rare epilepsies.

Advances in neuroscience have created a widening array of treatments for children with epilepsy. However, treating epilepsy requires an effective healthcare system to deliver these therapies. **Health services research** is a translational, multidisciplinary field that studies the delivery, organization, and financing of healthcare. This proposal applies health services research methods to improve care for children with epilepsy. Our **central hypothesis** is that we can lower emergency department (ED) visits, reduce healthcare costs, and improve seizure control for children with epilepsy by (1) predicting which children will become frequent ED visitors, and (2) providing those children with a care management intervention.

Pitfalls

- Omitted
- Not clear
- Too technical
- Not clearly impactful

PLAN, AIMS, and HYPOTHESIS.

Audience: A neuroscientist you don't know

Length: 2-4 sentences

Our central hypothesis is that text processing of clinical notes will improve surveillance and epidemiology of the rare epilepsies. We will use the NYC-CDRN to find affected individuals using EHRs from multiple centers. We will describe the incidence, prevalence, comorbidities, mortality, and insufficiency of ambulatory care for these individuals. Finally, we will develop, characterize, and disseminate a set of regular expressions that can find affected individuals via analysis of clinical notes.

The UH3 phase will use rigorous CER statistical techniques to manage observable selection bias, covariates, clustering of outcomes by site, repeated measures, loss to follow-up, and missing data. We will study outcomes at 24 months (Aim 1) and trajectories (Aim 2). Aim 3 will investigate effect heterogeneity,[50] based on preliminary data that the benefit of LEV over PB is magnified in the 40%[1] of infants with ELE due to a known cause (abnormal MRI, known gene).

PLAN, **AIMS**, and HYPOTHESIS.

Audience: A neuroscientist you don't know

Length: 1 perfect sentence. Sometimes a second sentence for key details.

Specific Aim 1: Develop and evaluate a predictive model to identify future frequent ED visitors (≥ 4 per year) among children with epilepsy, via machine learning techniques, using clinical and administrative data.

PLAN, AIMS, and **HYPOTHESIS**.

Audience: A neuroscientist you don't know

Length: 1 perfect sentence. Sometimes a second sentence for key details.

Hypothesis 2. A claims based case finding algorithm for infantile spasms will identify cases with better than 80% sensitivity, and better than 80% positive predictive value (PPV), compared to a chart review gold standard at four centers.

Aim 1 (Primary Outcomes): Compare the effectiveness of LEV vs. PB for: (a) seizure control on monotherapy; (b) cognitive development at age 24 months (Bayley-IV cognitive score); (c) epilepsy progression; and (d) mortality in a prospective, observational cohort of 350 infants age 1 month to 12 months with new-onset ELE, not including infantile spasms. *Seizure control on monotherapy* is seizure freedom for three months and no second ASM. *Epilepsy progression* includes emergence of slow spike and wave on EEG, tonic seizures, atonic seizures, epileptic spasms, or treatment resistance (ongoing seizures despite adequate trials of two ASMs[51]).

Hypothesis 1: Initial treatment with LEV (vs. PB) leads to superior seizure control on monotherapy, better cognition, lower risk of epilepsy progression, and decreased mortality, after accounting for observed selection bias, covariates, missing data, center variations, and loss to follow-up.

Aim 2 (Trajectories): Compare the effectiveness of LEV vs. PB on the trajectory of the following outcomes at ages 12, 18, and 24 months: seizure frequency, quality of life, sleep, and additional developmental domains (adaptive skills, language, motor, socio-emotional, and attention/executive function).

Hypothesis 2: Initial treatment with LEV (vs. PB) leads to better outcomes. The differences between treatments are apparent by age 12 months and persist at age 18 and 24 months.

Aim 3 (Effect Heterogeneity): Determine if epilepsy etiology is an effect modifier.

Hypothesis 3: Improvements in outcomes associated with LEV vs. PB selection for initial ELE monotherapy are more pronounced in infants with known etiology (i.e., abnormal MRI, known gene) vs. unknown etiology.

Pitfalls

- Dependent Aims (especially: Aim 1 develop test, Aim 2 apply test)
- New concepts appear without prior mention in introduction
- Not testable
- Fails FINER criteria (Feasible, Interesting, Novel, Ethical, Relevant)
- Wishy washy
- “We hope” (use “we expect”)
- Doesn’t start with a verb
- Insufficiently ambitious / Too ambitious

IMPACT.

Audience: Parents who fund research

Length: A brief paragraph

Impact. There are between 630 and 1770 new cases of infantile spasms per year in the US, and between 22,900 and 64,500 new cases worldwide.[14] Improving response rates by just 10% could dramatically improve an otherwise disabling, life-long epilepsy for hundreds of children per year in the US and thousands worldwide. The observation that 1 in 7 affected children are initially given therapies with inferior efficacy[11,15] underscores the pressing need to conduct and publish rigorous comparative effectiveness research and disseminate the findings. In addition, an accurate claims-based definition of infantile spasms will lay the foundation for several new domains of research into this disease: comparative effectiveness research, health services research, quality of care, epilepsy informatics, and surveillance and epidemiology.

Impact. Parents and caregivers tell clinicians that watching an infant have a first seizure is earth-shattering. “I thought my baby was dying,” they often tell us. Clinicians need evidence to select the best medication at the onset of epilepsy, balancing risks and benefits, before full diagnostic information is known.

IMPACT.

Audience: Parents who fund research

Length: A brief paragraph

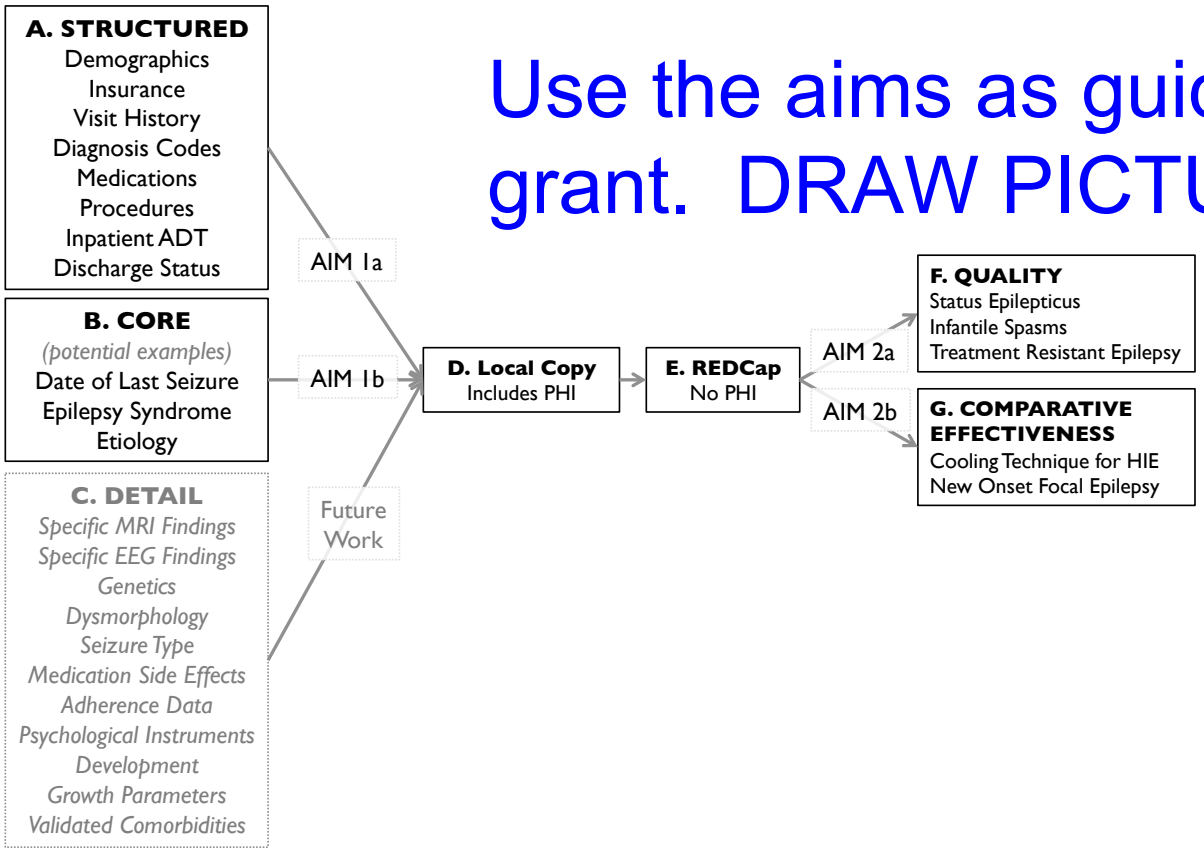
Impact. Improved epidemiological estimates will guide clinical care, prioritize research initiatives, spur development of therapies by industry, and help caregivers understand these devastating diseases. The regular expressions will help centers identify individuals with rare epilepsies to support surveillance, research, quality improvement, care management, and referral to advocacy organizations. This work aligns with recent IOM recommendations[21] (1, 2, 4, 8, 9, 13) and with the 2014 NINDS Epilepsy Benchmarks (IC, IIC, IIF, and IVD).

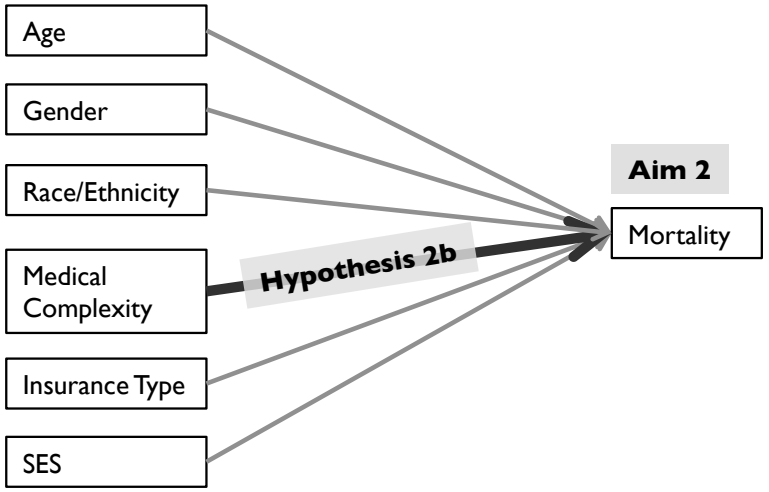
Pitfalls

- Omitted
- Not clear how work will improve human health
- Wishy washy

Then what?

Use the aims as guideposts throughout the grant. DRAW PICTURES





Final advice

- ~~Check it a lot~~
- ~~Kep checking it~~
- ~~Keep checking it~~
- ~~Rewrite it a lot~~
- ~~*Revise* it a lot~~
- ~~Revise~~
- ~~Revise!~~
- ~~Revise revise revise!~~
- revise Revise REVISE!!!!

Thank you!!!!