N-of-1 Trials in Children with Hypertension (NICHE)

NCT03461003

Version Date: 09/26/2019

N-of-1 Trials in Children with Hypertension (NICHE)

Joyce P. Samuel, Joshua A. Samuels, Adrienne K. Walton, Cynthia Bell, Charles Green

Abstract

Background: The single patient (n-of-1) randomized trial is an underused approach to resolving therapeutic uncertainty by using a patient's own data to inform an individualized treatment plan. A series of n-of-1 trials to select the preferred therapy in hypertensive children previously showed no single drug was selected for the majority of patients.

Purpose: To assess whether the n-of-1 trial approach improves blood pressure control while minimizing side effects, improving adherence, and patient satisfaction among hypertensive children.

Methods: Randomized clinical trial of hypertensive children (≥ 10 years old) treated at a UTH Pediatric Hypertension Clinic, and randomized to an n-of-1 trial or usual care, stratified by clinic site and relevant comorbidities.

Main outcome: Primary outcome: children with ambulatory blood pressure control at 6 months after enrollment. Secondary outcomes: mean blood pressure reduction from baseline, side effect experience, adherence, and patient satisfaction.

Conclusion: We have been unable to identify any published prior trial comparing use of n-of-1 trials to usual care for any disorder in pediatrics. Thus, our trial will advance learning about not only the treatment of pediatric hypertension but also the use of a neglected type of randomized trial to optimize the care of each patient.

Background

Pediatric hypertension, a growing problem, often requires prescription of antihypertensive medication. Often the case in special populations, pediatric hypertension specialists lack an evidentiary base for establishing definitive clinical practice guidelines on first-line therapies. Significant practice variation is an unsurprising consequence.[1] Routine choice of the same first-line therapy for most patients with primary hypertension, absent testing other options, may delay correction of blood pressure (BP) for months or years. Failure to incorporate patient preferences in medical decision-making may also contribute to decreased patient satisfaction and adherence.[2]

Large parallel-group, comparative effectiveness trials are likely not on the horizon for this population. Moreover, heterogeneity of treatment effects would minimize the generalizabilty of such a trial to all patients. Previously, we completed a series of n-of-1 randomized clinical trials to identify the preferred antihypertensive drug for children with primary hypertension based on BP reduction and absence of side effects.[3] In this sample (N=42) no single drug emerged as the preferred therapy for the majority of patients, amlodipine selected for 25%, lisinopril 50%, hydrochlorothiazide 12.5%.[4] Regarding the feasibility of this approach, we found that patients and parents readily accepted the concept of therapeutic uncertainty: 77% of eligible patients consented to participation in an n-of-1 trial. The acceptability of n-of-1 trials and differences in the preferred medication in our patient population

prompts consideration of whether this should become routine clinical practice for hypertensive children. We propose a parallel-group, randomized clinical trial (RCT) to test whether the n-of-1 trial approach is superior to usual care in achieving BP control while minimizing exposure to compliance reducing side-effects.

Objectives

Aim #1: Investigate whether among hypertensive children requiring pharmacologic therapy, participation in an n-of-1 trial results in improved BP control compared to usual care.

Hypothesis #1: Compared to the usual care group, the intervention group (n-of-1 trial) at 6 months will have 1) a higher proportion of patients with a BP less than the maximum normal ambulatory BP **(primary outcome)** and 2) a greater mean BP reduction from baseline.[5]

Aim #2: Determine whether the intervention group experiences a similar rate of medication side effects compared to the usual care group on the drug selected for treatment. **Hypothesis #2**: Participants in the n-of-1 arm will report equal or lower rates of side effects at 6 months compared to usual care.

Aim #3: Evaluate whether adherence and patient satisfaction at 6 months is higher in the intervention group than in the usual care group. **Hypothesis #3:** Participants in the n-of-1 arm will have greater adherence and patient satisfaction compared to usual care.

Aim #4. Evaluate the cost-effectiveness of the N-of-1 trial relative to usual care expressed as the incremental health system costs per additional normotensive child. **Hypothesis #4:** The N-of-1 trial will be deemed cost effective if it leads to either an increase in BP control without an increase in health system costs, a reduction in costs without a decrease in BP control, or both a reduction in costs with BP control improvement.

Exploratory Aim #5 : Develop a predictive model for subsequent use in a larger response adaptive randomization protocol. **Hypothesis #5** : A predictive model will more accurately identify the drugs most likely to provide benefit with minimal adverse effects for a participant with a given pattern of covariates.

Methods

Medications

Capitalizing on lessons learned from the previous sample of N=42 n-of-1 trial participants, this parallel-group RCT tests the superiority of an n-of-1 trial relative to usual care in achieving BP control. Among the three drugs tested (amlodipine, hydrochlorothiazide (HCTZ), and lisinopril), HCTZ was least likely to be the preferred drug and the most likely to be associated with intolerable side effects.[4] Therefore, in the current study we will first test amlodipine against lisinopril.

The initial series of n-of-1 trials was designed to identify only whether maximal doses of a *single* drug could control BP, however 12.5% of patients remained uncontrolled on monotherapy. The current n-of-1 trial includes an option to add HCTZ as a second agent if optimal BP control is not achieved with high doses of a single drug.

Previously we excluded patients with chronic kidney disease (CKD), proteinuria, and/or diabetes mellitus (DM). For these patients, an ACE-inhibitor (ACEi) or an angiotensin-receptor blocker (ARB) is recommended as first-line monotherapy for renal protective effects.[6] BP control is particularly important for these children who are at higher risk for adverse cardiovascular outcomes. The current trial includes these patients using a restricted protocol, testing losartan (ARB) against lisinopril (ACEi), and allows the addition of HCTZ.

Setting

UTH Pediatric Hypertension Clinic in the Texas Medical Center and 3 greater Houston satellite locations. Three hypertension specialists (co-investigators JPS, JAS, AKW) practice across all sites.

Inclusion/Exclusion criteria

Inclusion: treating physician determines that pharmacologic therapy is indicated to treat hypertension

Exclusion criteria: 1) age < 10 years, 2) resistant hypertension (requiring ≥ 3 drug therapy), 3) absolute contraindication or allergy to any of the tested drugs.

Recruitment

Clinic schedules will be reviewed by the PI, and potentially eligible patients will be identified. Eligible families will receive a one page information sheet during a clinic visit and a discussion with the treating physician with an offer of a second discussion with the PI.

Consent

The Committee for the Protection of Human Subjects of McGovern Medical School (HSC-MS-17-1014) and Harris Health approved the protocol, and patients provide verbal informed consent after reviewing a one page information sheet. The trial is registered on clinicaltrials.gov (NCT03461003).

Randomization

Randomization will be assigned using the online REDCap randomization module, stratified according to comorbidities at baseline (CKD/proteinuria/DM vs all others) and clinic site (4 total) resulting in 8 strata.[8] Treatment assignment will be determined through REDCap, maintaining allocation concealment. For those allocated to the intervention arm, a second randomization will determine the sequence of treatment periods based on a computer generated random number list which will also be maintained and communicated via REDCap.

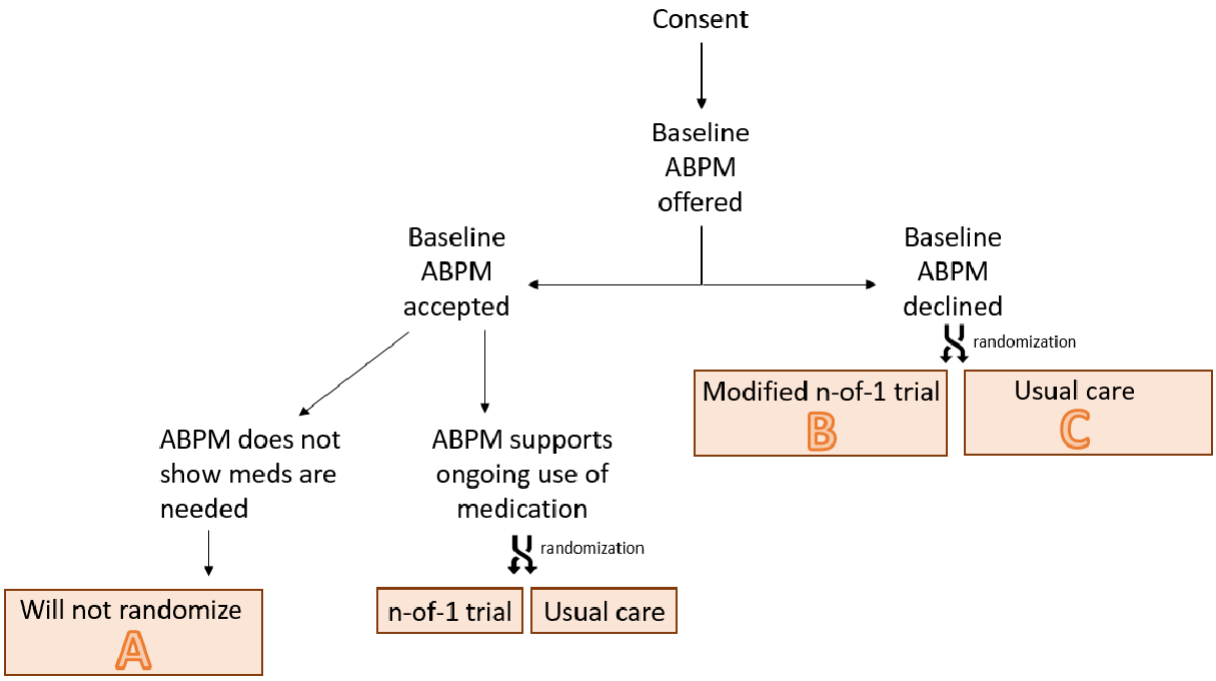
Those with CKD, proteinuria, and DM will be randomized 1:1 to usual care or the restricted n-of-1 protocol. All others will be randomized 1:1 to usual care or the unrestricted protocol.

- Restricted protocol: Includes patients with comorbidities for which an ACE-I or ARB is recommended as first line therapy [6]
    - Drug A: lisinopril
    - Drug B: losartan
    - Drug C: HCTZ

- Unrestricted protocol: Includes patients for whom no particular drug class is indicated based on comorbidities (most pediatric patients with primary hypertension)
    - Drug A: lisinopril
    - Drug B: amlodipine
    - Drug C: HCTZ

In both arms, if ambulatory hypertension has not been confirmed (off meds) within 12 months of enrollment, then this will be performed prior to proceeding to the next step.

After consent but prior to randomization, a 2 week test off medication and baseline ABPM is offered (if not already done within 12 months of enrollment). It will be described as optional, and decision will be based on preferences of the treating physician and the patient/family.



The protocol will be adjusted for each scenario as follows:

A. Blood pressure will be monitored with repeated 24 hour ABPM at regular intervals thereafter (q 3 months) to verify they remain normotensive.
    i. If the BP is noted revert to hypertensive and pharmacologic therapy becomes indicated, then they will be randomized

B. Patients will be treated according to the n-of-1 trial protocol, modified as follows for the lack of baseline BP. If BP is noted to be well controlled with the lowest doses of both medications

tested, then the family and treating physician will be notified. At that point, they will be given another opportunity to consider a 2 week test off medication and baseline ABPM.

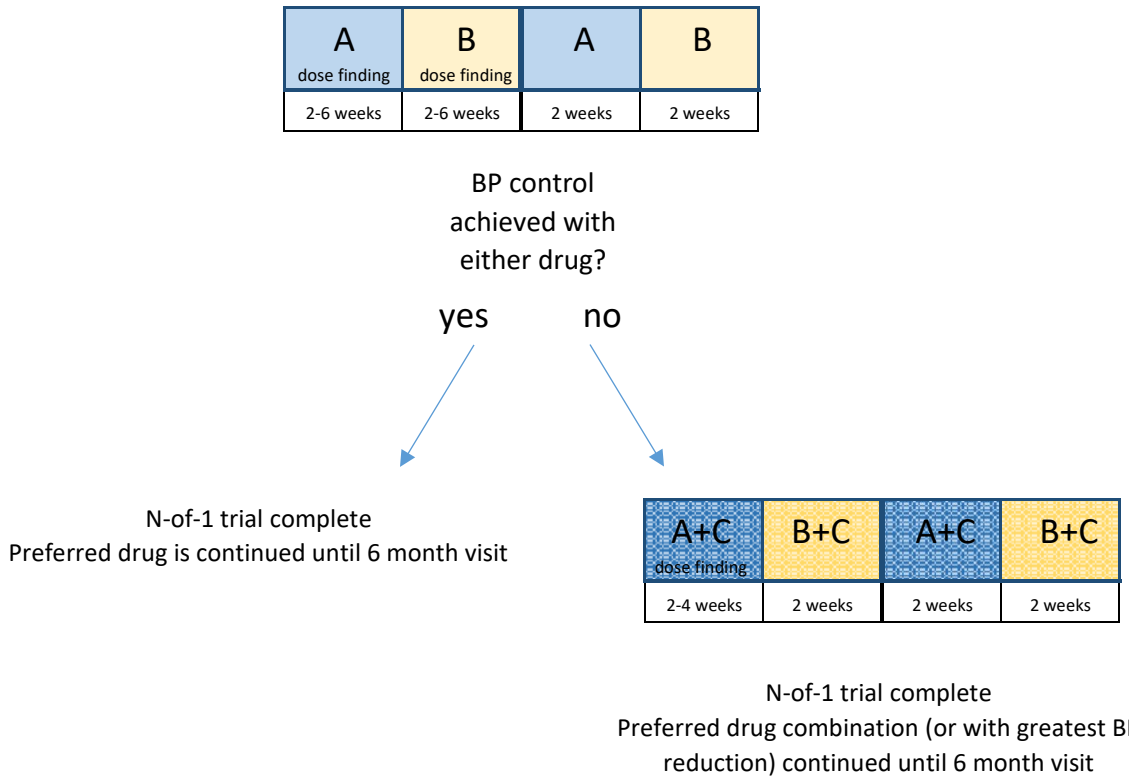
i. If the baseline ABPM is declined, then they will continue the n-of-1 trial protocol.

ii. If it is accepted, and they are found to be normotensive, then they will be followed with ABPM at q 3 month intervals thereafter until the 6 month final outcome assessment visit. However if the baseline ABPM shows they are in fact hypertensive, they will continue the n-of-1 trial protocol.

C. Patients will be treated according to physician preference as described in the control arm section of the protocol.

Intervention (n-of-1) arm:

Participants randomized to the intervention arm will receive a one page concept sheet outlining the procedures for the n-of-1 trial. Each n-of-1 trial consists of at least four 2-week treatment periods (2 paired sets) to test 2 drugs in randomized order. The first treatment period for each drug constitutes a 'dose-finding' period, ending when BP control is achieved or maximum dose is reached. Initial, low weight-based dosing, may increase according to a predefined schedule every two weeks during the dose-finding period. Failure to achieve BP control at maximum doses of either drug will result in augmentation with a second agent. Combination therapy will require an additional four 2-week treatment periods in randomized order.



Assessment of BP control (in n-of-1):

- Determination of BP control (defined by AHA criteria) will be at the end of each 2 week period using 24 hr ambulatory BP monitor (ABPM) which will be mailed to and from the patient's home in a prepaid box. [5] This minimizes the inconvenience associated with repeated clinic visits (time off work/school and transportation costs)- a common reason for refusal to participate in the initial series, and will also decrease clinic space and staff requirements, which may improve the generalizability of this protocol to other centers.
- Side effect tolerability assessed every 2 weeks using questionaires, via REDCap, piloted in the previous series of n-of-1 trials.

Determination of preferred drug (in n-of-1):
Preferred drug is that which reduces the ambulatory BP the most (average BP reduction across both treatment periods in which it was tested) without intolerable side effects.

Control arm

Participants randomized to the control arm will receive a one page concept sheet with generic information about blood pressure management. No protocol will be introduced to standardize BP management in the control arm. Physicians will continue their usual practice with regard to drug choice and dose, BP measurement modality, and intervals between visits. Each treating physician will be asked to maintain their usual practice for the course of the study unless emerging published evidence during the study period justifies a practice change. Review of clinic notes in the electronic medical record will permit documentation of BP management for each patient.

Outcome measurement

Aim #1: 24 hr ABPM performed 6 months after randomization will determine if BP is less than maximum normal BP as defined by AHA criteria, and mean BP reduction from baseline.[5] Outcome assessor will be blinded to treatment arm.

Aim #2: Side effect survey* at the 6 month visit will evaluate the overall burden of side effects since enrollment (different from the biweekly questionaires in treatment arm). Routine bloodwork (complete metabolic panel) will be checked within 2-4 weeks of starting lisinopril, losartan, or HCTZ, as per usual practice. Serious adverse effects will include (not limited to) increase in serum creatinine by >20% , potassium level > 5.5 mmol/L or < 3.5 mmol/L, or magnesium < 1.7 mg/dL prompting drug discontinuation.

Aim #3: Satisfaction survey* at the 6 month visit will assess parent rating of outpatient care. [9] Adherence will be approximated with pill count at 6 month visit, in which current bottle is assessed to determine the difference between actual number missing pills versus expected missing based on bottle label fill date.

*administered by a nurse blinded to treatment arm

Aim#4: The acquisition costs for the BP drugs will be based on the average wholesale price as listed in the Micromedex Red Book. The costs for any hypertension-related hospitalizations and ED visits occurring within our system will be estimated based on Memorial Hermann Hospital System (MHHS) billings by multiplying hospital charges by department-specific cost-to-charge ratios. The costs for any reported hospitalization and ED visit utilized outside our system will be based on the mean cost per bed-day and ED visit occurring in the MHHS among our patient sample. The costs for outpatient care will be based on the standard RVU method and augmented by the ABPM costs (i.e. equipment costs and personnel time cost). All costs will be inflated to the year of the analysis based on the consumer price index for medical services.

Exploratory Aim #5: Evaluation of the accuracy of the predictive model will utilize Breier scores and area under the ROC curve.[10-12]

General Analytic Approach

The data analytic strategy will use generalized linear multilevel modeling with level-two random effects accounting for clustering of participants within site, and where applicable, observations within

participants. Modeling will use R v. 3.4 and Stan v. 1.10.[13, 14] In evaluating the comparability of groups, a posterior probability of > 95% will constitute evidence for statistically reliable differences. Baseline or demographic variables on which group differences are detected, and which are correlated with outcomes, meet the definition of confounders [15, 16] and will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not. This will permit determination of the degree to which any group differences might confound conclusions regarding treatment. All analyses will follow intention-to-treat principles. Joint modeling of observed outcomes and missing data will address missingness. [17] Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods [18]. Convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain will be assessed via graphical (Gelman-Rubin Plots) and quantitative (Gelman-Rubin Diagnostics and Effective Sample Size) evidence. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Specification of diffuse, neutral priors will reflect the initial uncertainty regarding effect sizes. For all generalized linear multilevel models, priors for regression coefficients will be specified as ~Normal (μ=0, σ2=100) on the identity or log-scale depending upon the model, level one error variances will be specified as ~Half-T (df = 3, mean = 0, standard deviation = 100). Prior distributions for level two variances will use ~Half-T (df = 3, mean = 0, standard deviation = 100). Priors for the comparison of proportions will be specified as ~Beta (α=0.5, β=0.5). To the degree possible we will also evaluate informative priors based on the previous n-of-1 trial.

Economic evaluation

Cost differences between treatment groups will be assessed using multilevel generalized estimating equation (GEE) models with log-link and gamma distribution. The cost models will be adjusted for comorbidities at baseline (CKD/proteinuria/DM vs all others) and within-site correlation. These analyses will be performed using Stata software version 15.1 (StataCorp).

Sample Size

The purpose of the current study is to provide the most precise, unbiased estimates of treatment effect possible given the constraints imposed by budget and logistic (e.g. recruitment) considerations. As such we plan to do the largest possible trial within these constraints. Recruiting participants at 4 sites with fewer exclusion criteria than in the previous n-of-1 trial series, we anticipate credibly accruing N = 80 participants over the course of the 18 month study (1-2 per week, with 20% dropout rate). With 1:1 randomization (stratified by site and protocol subtype) we expect n = 40 per condition. We expect a relatively large change in the primary outcome of the proportion of participants achieving BP control. Among usual care participants, we anticipate a 50% control rate at 6 months.[19] The control rate of the preliminary n-of-1 trial series was 80% at 3 months. Anticipating some decrement in the proportion of participants with BP under control we might still expect a relatively large treatment effect with 75% of n-of-1 trial participants achieving control; an absolute increase of 25%.

Feasibility

Having previously demonstrated the feasibility of conducting n-of-1 trials, the current study will follow a similar protocol with the addition of randomizing to n-of-1 or usual care, and monitoring of those in usual care. A nationally recognized pediatric hypertension center, our Division is well recognized for

successfully completing challenging studies at the forefront of epidemiologic studies to establish prevalence data and is an ABPM coordinating site for the nation's largest multicenter prospective cohort study in children with CKD.

Contribution to LHC at UTH

We will design a multi-center national RCT to test the benefit of this approach, to be submitted under PCORI Funding Announcement: Pragmatic Clinical Studies to Evaluate Patient-Centered Outcomes. This larger trial will evaluate whether this approach is feasible and effective in other centers, as well as whether the cost of n-of-1 time/personnel justifies the benefits: improved BP control, increased patient satisfaction, and decreased burden of cardiovascular complications. Finally in a proposed, large multi-center trial we would include as a comparison group a response adaptive n-of-1 randomization approach based on predictive probabilities, evaluating it relative to the standard n-of-1 care and treatment as usual.

We hope that this prompts a thoughtful discussion on the overlap between medical and research ethics. The learning healthcare system ethics framework proposed by Faden and colleagues challenges clinicians to consider their moral obligation to integrate continuous learning activities while striving to provide optimal care. This randomized trial represents a rigorous assessment of whether one such type of learning activity (n-of-1 trials) can improve patient care for a major disorder presenting in childhood known to increase major morbidity and mortality in adulthood.

References

1. Yoon, E.Y., et al., *Antihypertensive prescribing patterns for adolescents with primary hypertension.* Pediatrics, 2012. **129**(1): p. e1-8.

2. Mulley, A.G., C. Trimble, and G. Elwyn, *Stop the silent misdiagnosis: patients' preferences matter.* BMJ, 2012. **345**: p. e6572.

3. Samuel, J.P., et al., *Comparative effectiveness of antihypertensive treatment for older children with primary hypertension: study protocol for a series of n-of-1 randomized trials.* Trials, 2016. **17**: p. 16.

4. Samuel, J.P., et al., *Selection of first-line therapy in children with primary hypertension: a series of n-of-1 trials.* Unpublished manuscript.

5. Flynn, J.T., et al., *Update: ambulatory blood pressure monitoring in children and adolescents: a scientific statement from the American Heart Association.* Hypertension, 2014. **63**(5): p. 1116-35.

6. Flynn, J.T., et al., *Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents.* Pediatrics, 2017. **140**(3).

7. Samuel, J.P., et al., *Randomized n-of-1 Trials: Quality Improvement, Research, or Both?* Pediatrics, 2016.

8. *REDCap Randomization Module.* https://apps.icts.uiowa.edu/confluence/display/REDCapDocs/REDCap+Randomization+Module#REDCapRandomizationModule-EnablingtheRandomizationModule.

9. US Department of Health and Human Services; Agency for Healthcare Research and Quality. CAPHS: surveys and tools to advance patient-centered care. http://www.CAHPS.AHRQ.gov.

10. Brier, G.W., *Verification of Forecasts Expressed in Terms of Probability.* Mon. Wea. Rev., 1950. **78**: p. 1-3.

11. Murphy, A.H., *A New Vector Partition of the Probability Score.* Journal of Applied Meterology, 1973. **12**: p. 595-600.

12. Steyerberg EW, V.A., Cook NR, et al., *Assessing the performance of prediction models: a framework for traditional and novel measures.* Epidemiology, 2010. **21**: p. 128-38.

13. Team, R.C., *R: A Language and Environment for Statistical Computing*. 2017, R Foundation for Statistical Computing: Vienna, Austria.

14. Team., S.D., *RStan: the R interface to Stan: Stan Development Team*. 2017, Available from: http://mc-stan.org .

15. Assmann, S.F., et al., *Subgroup analysis and other (mis)uses of baseline data in clinical trials.* Lancet, 2000. **355**(9209): p. 1064-9.

16. Pocock, S.J., et al., *Subgroup analysis, covariate adjustment and baseline comparisions in clinical trial reporting: Current practice and problems.* Statistics in Medicine, 2002. **21**: p. 2917-2930.

17. Best, N. and A.E.p.-. Thomas, *Bayeisan Graphical Models and Software for GLMs*, in *Generalized Linear Models: A Bayesian Perspective*, D. Dey, S.K. Ghosh, and B.K. Mallick, Editors. 2000, Marcel Dekker, Inc.: New York.

18. Fitzmaurice, G.M. and N.M. Laird, *Generalized linear mixture models for handling nonignorable dropouts in longitudinal studies.* Biostatistics, 2000. **1**: p. 141-156.

19. Seeman, T. and J. Gilik, *Long-term control of ambulatory hypertension in children: improving with time but still not achieving new blood pressure goals.* Am J Hypertens, 2013. **26**(7): p. 939-45.

Appendix 1. Specific Analyses

Aim #1: Analysis 1.a. Controlling for stratification variables and accounting for correlation due to clustering within center using a level-two random intercept, multilevel logistic modeling will evaluate the proportion of participants achieving improved BP control, defined by by AHA criteria [5], both SBP and DBP (throughout wake and sleep) less than the 95th%ile based on the patient's gender and height, as a function of treatment. **Analysis 1.b.** Controlling for stratification variables and accounting for correlation due to clustering within center using a level-two random intercept, multilevel linear models will separately evaluate the levels of systolic and diastolic BP as a function of treatment.

Aim #2: Analysis 2.a. Controlling for stratification variables and accounting for correlation due to clustering within center using a level-two random intercept, multilevel logistic modeling will evaluate the probability of experiencing a severe adverse event, defined by changes in bloodwork that prompt discontinuation of the medication, as a function of treatment. **Analysis 2.b.** Controlling for stratification variables and accounting for correlation due to clustering within center using a level-two random intercept, multilevel modeling for count data (e.g. Poisson, Negative Binomial, Zero-Inflated

distributions, etc.) will evaluate the number of adverse events, defined by any side effect reported by the patient at the 6 month visit or any serious adverse event as defined above, as a function of treatment. **Analysis 2.c.** Descriptive analyses will characterize the distribution and types of reported adverse events as a function of treatment.

Aim #3: Analysis 3.a. Controlling for stratification variables and accounting for correlation due to clustering within center using a level-two random intercept, multilevel modeling will evaluate patient satisfaction scores as a function of treatment. **Analysis 3.b.** Controlling for stratification variables and accounting for correlation due to clustering within center using a level-two random intercept, multilevel modeling for count data (e.g. Poisson, Negative Binomial, Zero-Inflated distributions, etc.) will evaluate the number of doses taken with an offset variable to represent the number of doses that should have been taken as a function of treatment.

Aim #4: Analysis 4.a. Beginning with informative priors derived from the preliminary n-of-1 trial data described above, Bayesian multilevel modeling will estimate the predicted probability that each new participant will experience a therapeutic response (i.e. combination of BP control and tolerability of side effects) as a function of baseline covariates. Comparison of these predictions to observed outcomes will permit evaluation of accuracy and discrimination using Breier scores and area-under the ROC curve.[10-12] Each newly ascertained outcome will then update the posterior distribtution for subsequent predictions. Predictive distributions from accruing data offer the potential of shorter, more efficient n-of-1 trials; precise predictions may minimize the number of times or compounds through which a given participant must iterate to achieve BP control with minimal side-effects We envision a larger randomized controlled trial in which one of the conditions tested would adjust within-participant randomization to potential drugs based on the normalized (i.e. to sum to one) predicted probability of success for each drug. While these predicted probabilities will not influence decision-making in the current trial, we anticipate estimates associated with this aim will permit simulations that can determine the potential gains in efficiency for converging on the best treatment using an adaptive, versus non-adaptive n-of-1 algorithm.