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Quartet USA
Quadruple UltrA-low-dose tReaTment for hypErTension

The Story of **QUARTET USA**: a phase II, double-blind randomized controlled trial

from a biostatistician's perspective

Quadruple UltrA-low-dose tReaTment for hypErTension

MPIs:
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March 31, 2023

Access Community Health Network
TRANSFORMING COMMUNITY HEALTH CARE

The University of Sydney

The George Institute for Global Health

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Disclaimer:
These views are my own.

I have no relevant conflicts of interest.

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How it all started…

(in 2016 – about 6.5 years ago!)

Early October 2016…

Hi Jody!
I am putting together an **R61/R33 proposal to NHLBI due November 10** to evaluate the effect of an ultra-low dose four-drug combination blood pressure lowering pill on blood pressure compared with monotherapy at 12 weeks among individuals with uncomplicated hypertension through a network of federally qualified health centers in Chicago (ACCESS).

This new R61/R33 mechanism … and I wanted to see if you might be interested in working together on this given your biostatistical experience in randomized trials.

The overall idea came from Clara Chow at The George Institute for Global Health in Sydney, and she already has funding for a trial in Australia that is in the preparatory phase.

…I'm interested. What do you think you'll need from my end? I'm assuming we'd need to meet to discuss details?

... It may be tricky making schedules work, but I think we can do it ;)

Funding Opportunity Announcement (FOA): PAR-16-405

Institute: NHLBI

Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Heart, Lung, and Blood Institute (NHLBI)
Funding Opportunity Title	Single-Site Investigator-Initiated Clinical Trials (R61/R33)
Activity Code	R61/R33 Exploratory/Developmental Phased Award
Announcement Type	New
Related Notices	• October 25, 2017 - This PAR has been reissued as PAR-18-406. • June 14, 2017 - Clarification of NHLBI Policy Regarding Submission of Phase II and Beyond Clinical Trials Applications. See Notice NOT-HL-17-519. • May 31, 2017 - Revision: NHLBI Policy for Submission of Investigator-Initiated Single-Site Clinical Trials (Phase II and beyond). See Notice NOT-HL-17-518. • May 10, 2017 - New NIH "FORMS-E" Grant Application Forms and Instructions Coming for Due Dates On or After January 25, 2018. See NOT-OD-17-062. • September 19, 2016 - Notice of Availability of Frequently Asked Questions for PAR-16-405. See Notice NOT-HL-16-450. • August 25, 2016 - New NHLBI Policy: Investigator-Initiated Single-Site Clinical Trials (Phase II and beyond). See Notice NOT-HL-16-336.

This FOA is applicable to single site clinical trials that are phase II and above. For the purposes of this FOA, the definition of a single site clinical trial is one in which the protocol is implemented by one investigational site that conducts and coordinates the protocol. While a single site clinical trial may enroll participants from multiple locations/clinics within a geographic area, those participants will receive an intervention or undergo outcome assessments under the direction and oversight of one research team at one investigational site.

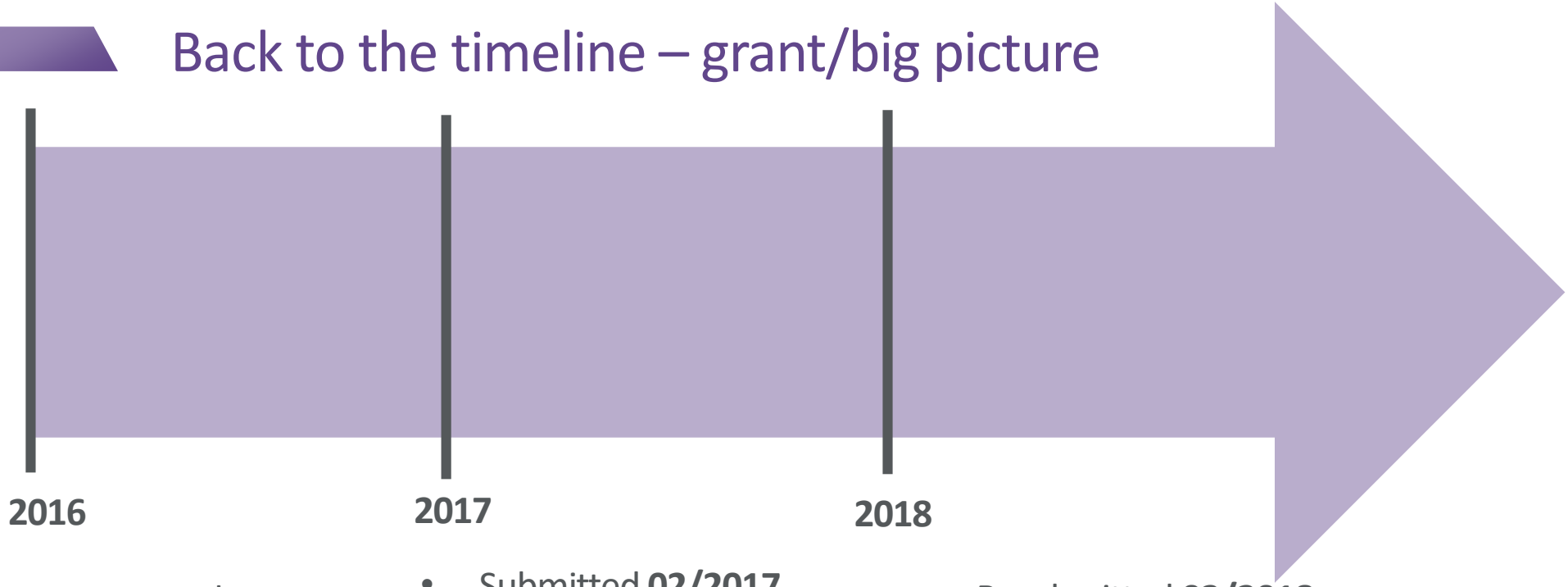
Proposed clinical trials may utilize a design anywhere along the continuum between explanatory and pragmatic. For this FOA, pragmatic trials are considered those that test an intervention under the usual clinical conditions in which it will be applied, while explanatory trials do so under more idealized circumstances. The trial design should be appropriate for the study question.

Structure

This FOA is intended to support Phase II or above single site clinical trials. This FOA will utilize a bi-phasic, milestone-driven R61/R33 mechanism consisting of a start-up phase (R61) and a full enrollment and clinical trial execution phase (R33). Applicants must address objectives for both a R61 and a R33 phase and are strongly encouraged to use project management principles as appropriate.

- This was a new type of award (R61/R33)
- Two phases
  - R61: startup phase
  - R33: enrollment
- Milestone driven
- Ultimately decided on MPI setup (Mark: contact PI)

Back to the timeline – grant/big picture



- Put together application
- Webinar with NHLBI to request higher budget

- Submitted **02/2017**
- **06/2027 –** score of 28 (not bad ☺, unsure on "pay line")
- Pre-IND meeting with the FDA
- Worked on plans for resubmission + responses to reviewers

- Resubmitted **03/2018**
- "no promises, but there is reason for hope. Nothing to lose by submitting the A1, but I am now optimistic that QUARTET will be funded."
- **06/2018:** Notice of Award received! (based on 1st submission)

Taking a step back…

What are we trying to do in this study?

Rationale (from the protocol)

Elevated blood pressure, also known as hypertension when **>130/>80 mmHg**, is a **leading cause of preventable morbidity and mortality globally**.

In the **United States, nearly half of adults**, have hypertension, and prevalence rates are rising.

While **most Americans are aware of their hypertension** and while most of those who are aware **receive treatment (75%)**, **less than half (47%) are controlled using a goal blood pressure of <130/<80 mmHg.**

Typical plan for treatment includes: **repeated clinic visits** with **repeated dose titrations** of **multiple individual** drugs → this is challenging (for both patients and providers).

Additional limitation: maximizing doses of individual drugs leads to a **greater risk of side effects**.

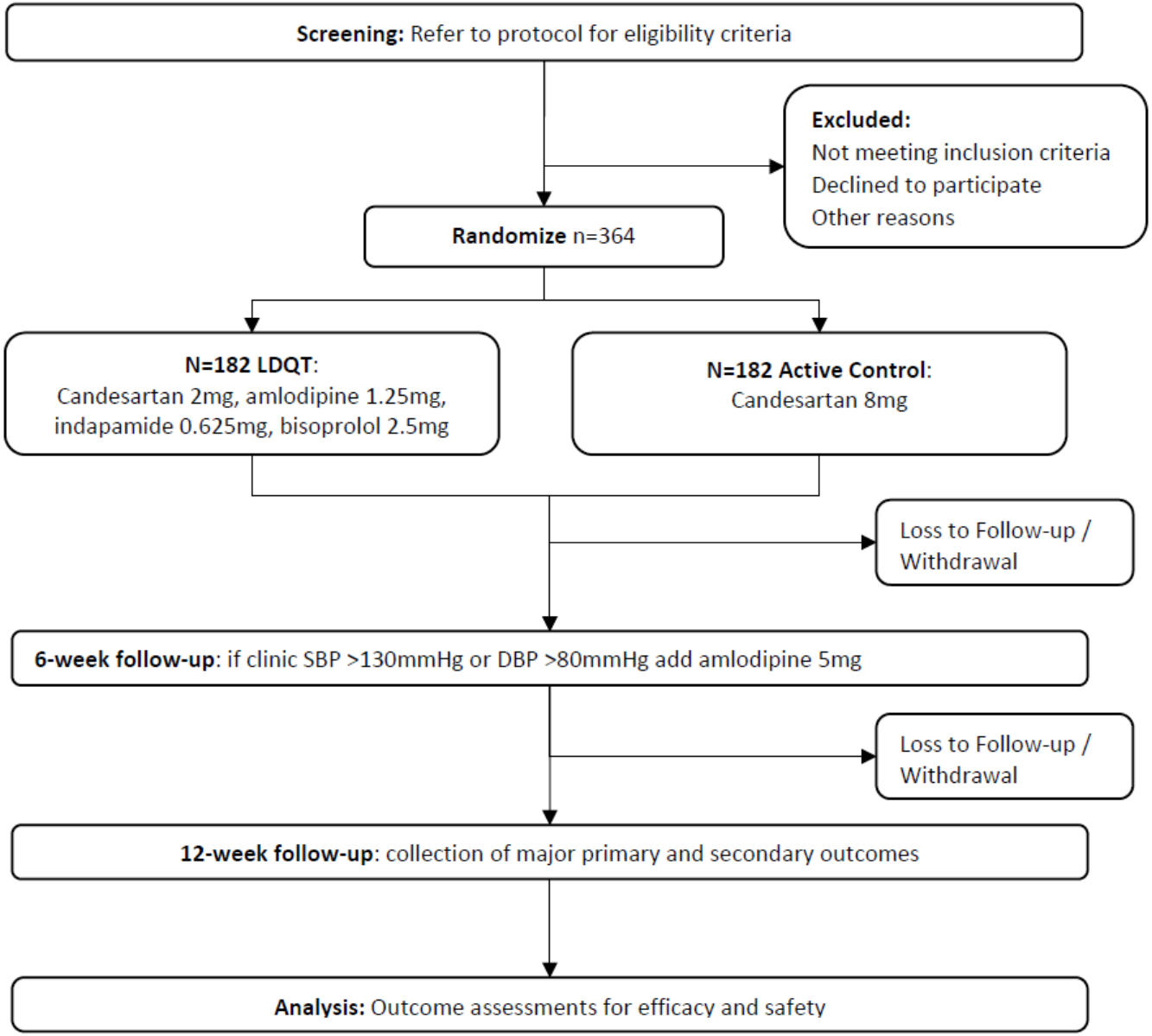
Objective

QUARTET USA (inspired by QUARTET – original study in Australia)

- To investigate, in a double-blind randomized controlled trial, whether initiating treatment with ultra-low-dose quadruple-combination therapy ("LDQT") will lower office blood pressure more effectively, and with fewer side effects, compared to initiating standard dose monotherapy in patients with hypertension.

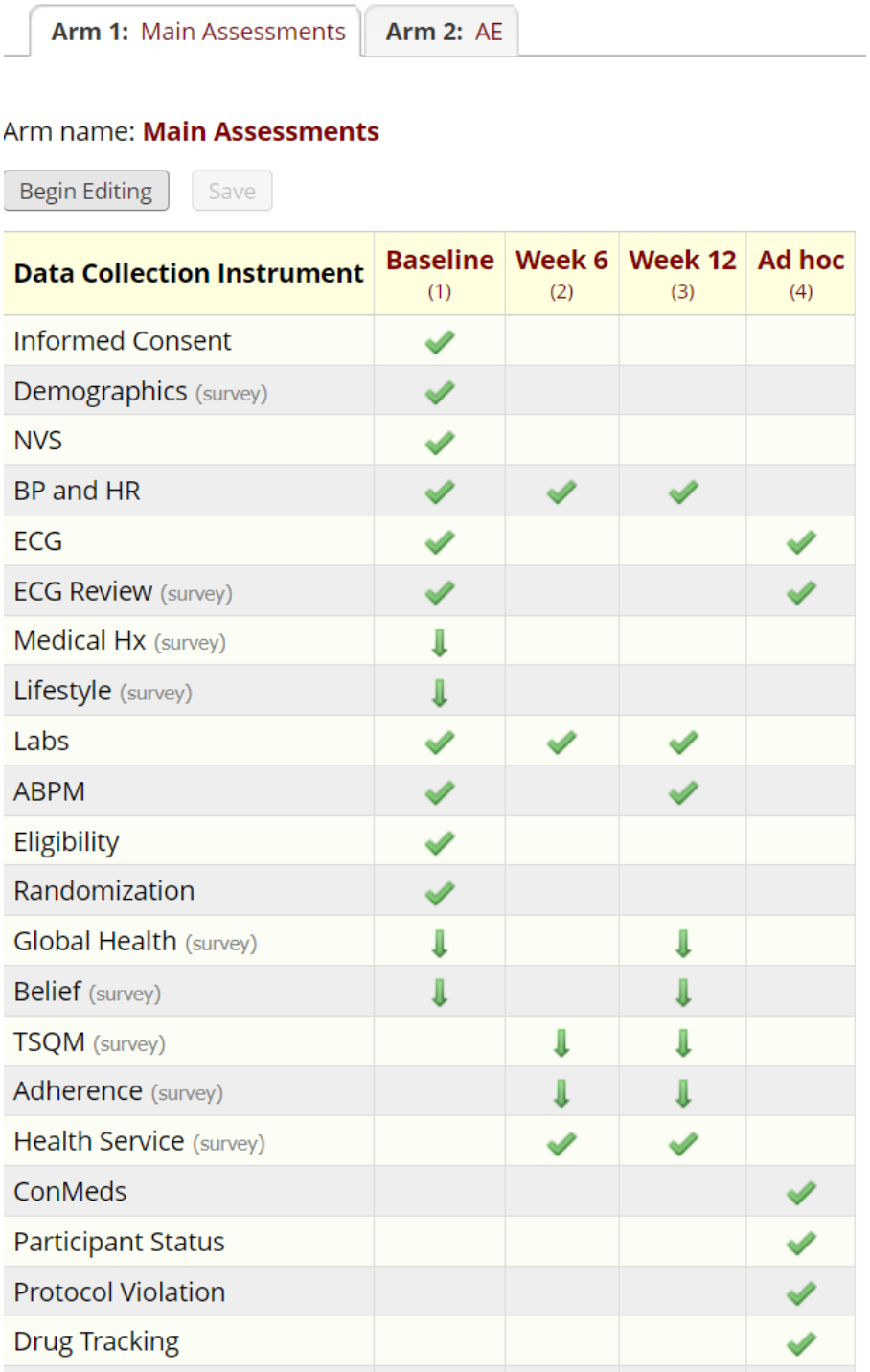
- **Primary hypothesis**: A combination pill comprising **four types of blood pressure lowering medications**, each at one-quarter standard doses, will lower office blood pressure more effectively than initiating patients with standard dose monotherapy in patients with hypertension.

Figure 2. Study Schematic



A view of the database →

(note there are two “arms” within REDCap)



Arm 1: Main Assessments | Arm 2: AE

Arm name: **Main Assessments**

Begin Editing | Save

Data Collection Instrument	Baseline (1)	Week 6 (2)	Week 12 (3)	Ad hoc (4)
Informed Consent	✓			
Demographics (survey)	✓			
NVS	✓			
BP and HR	✓	✓	✓	
ECG	✓			✓
ECG Review (survey)	✓			✓
Medical Hx (survey)	↓			
Lifestyle (survey)	↓			
Labs	✓	✓	✓	
ABPM	✓		✓	
Eligibility	✓			
Randomization	✓			
Global Health (survey)	↓		↓	
Belief (survey)	↓		↓	
TSQM (survey)		↓	↓	
Adherence (survey)		↓	↓	
Health Service (survey)		✓	✓	
ConMeds				✓
Participant Status				✓
Protocol Violation				✓
Drug Tracking				✓

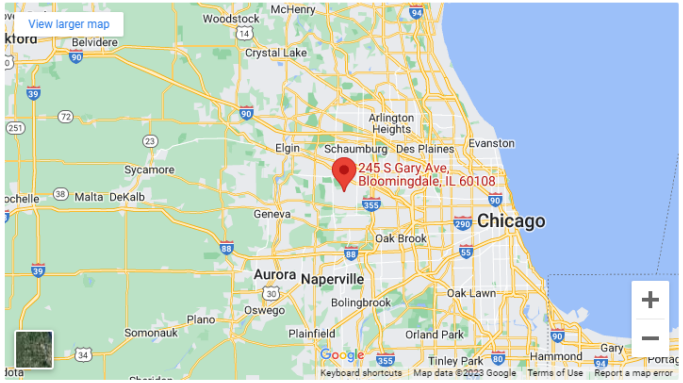
Study Participants

Patients within Access Community Health Network

ACCESS COMMUNITY HEALTH NETWORK
TRANSFORMING COMMUNITY HEALTH CARE

- https://www.achn.net/

ACCESS Martin T. Russo Family Health Center



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Wednesday: 8:00 a.m. - 8:00 p.m.
Thursday: 8:00 a.m. - 8:00 p.m.
Friday: 8:00 a.m. - 5:00

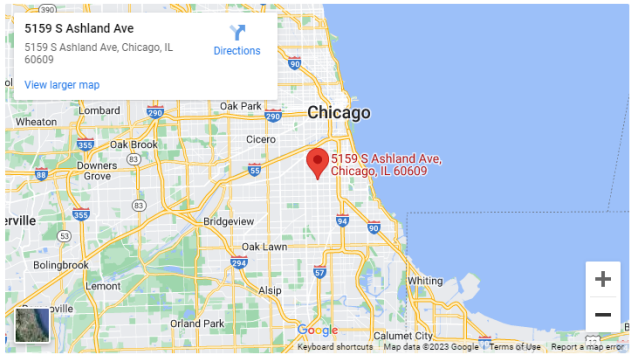
Doctors and other Medical Providers

Family Medicine
- Charity Alikpala, D.O.
- Preyanshu Parekh, D.O.
- Steven Miguel Chapa, P.A.-C.
- Marion R. Tan, F.N.P.-B.C.
- Mary Winokur, P.A.-C.
- Nicole Locascio, P.A.-C.
- Joy De Leoz, M.D.

Obstetrics and Gynecology
- Jessica Ocampo, M.D.
- Dale Liaugminas, M.D.
- James Kim, M.D.
- Josephine Rios, C.N.M.

Internal Medicine
- Jairo Mejia, M.D.

ACCESS Ashland Family Health Center



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Doctors and other Medical Providers

Psychiatry
- Motaz Alshami, M.D.
- Jorge Luis Castillo-Gonzalez, M.D.

Family Medicine
- Victoria Viveen, P.A.-C.
- Katie McKeough, P.A.-C.

Obstetrics and Gynecology

Pediatrics
- Brett Ballard, M.D.
- Daneen Woodard, M.D.

Internal Medicine
- Eleanor Teoh, D.O.
- Daneen Woodard, M.D.

Cardiology

Inclusion / Exclusion Criteria

Inclusion

- Adults (≥18 years)
- Spanish or English speaker
- Blood pressure within range for Stage I hypertension as defined in protocol

	SBP lower limit, mmHg	SBP upper limit, mmHg	DBP lower limit, mmHg	DBP upper limit, mmHg
Automated office (clinic) measurement within the last 12 weeks, untreated	140	179	90	109
Automated office (clinic) measurement within the last 12 weeks, on monotherapy	130	159	85	99
Research grade blood pressure measurement in QUARTET Australia	No limit	No limit	No limit	No limit
Research grade blood pressure measurement (baseline mean)	115	None	60	None

Inclusion / Exclusion Criteria

Exclusion

- Known **contraindication** to candesartan, amlodipine, indapamide or bisoprolol.
- Previous diagnosis of **coronary artery disease, stroke, or heart failure**.
- Presence of significant **proteinuria.**
- Evidence of **secondary cause** of hypertension.
- Women who are **pregnant, breast feeding or of childbearing potential** and are not using and do not plan to continue using medically acceptable form of contraception throughout the study.
- Concomitant illness, physical impairment or mental condition which in the **opinion of the study team / primary care physician could interfere** with the conduct of the study including outcome assessments.
- **Participation in a concurrent interventional medical investigation** or pharmacologic clinical trial.
- Participant's **responsible primary care or other responsible physician believes it is not appropriate** for participant to switch current monotherapy.
- Inability or unwillingness to provide written informed consent.
- Unable to complete study procedures.

Outcomes

Primary Outcome

Automated office systolic blood pressure (SBP) at 12 weeks, and analyses will compare this change across arms for primary outcome analyses, adjusting for baseline.

Secondary Outcomes

a. Automated office diastolic blood pressure (DBP) at six and 12 weeks.
b. Proportion of patients with hypertension control (SBP < 130 mmHg and DBP <80 mmHg) at six and 12 weeks.
c. Proportion of patients requiring step-up treatment.
d. Proportion of patients with adverse event-free hypertension control (SBP < 130 mmHg and DBP < 80 mmHg).
e. Medication Adherence (pill counts, participant-report).
f. Health-related Quality of Life: PROMIS Global Health.

Sample Size Calculations – Original

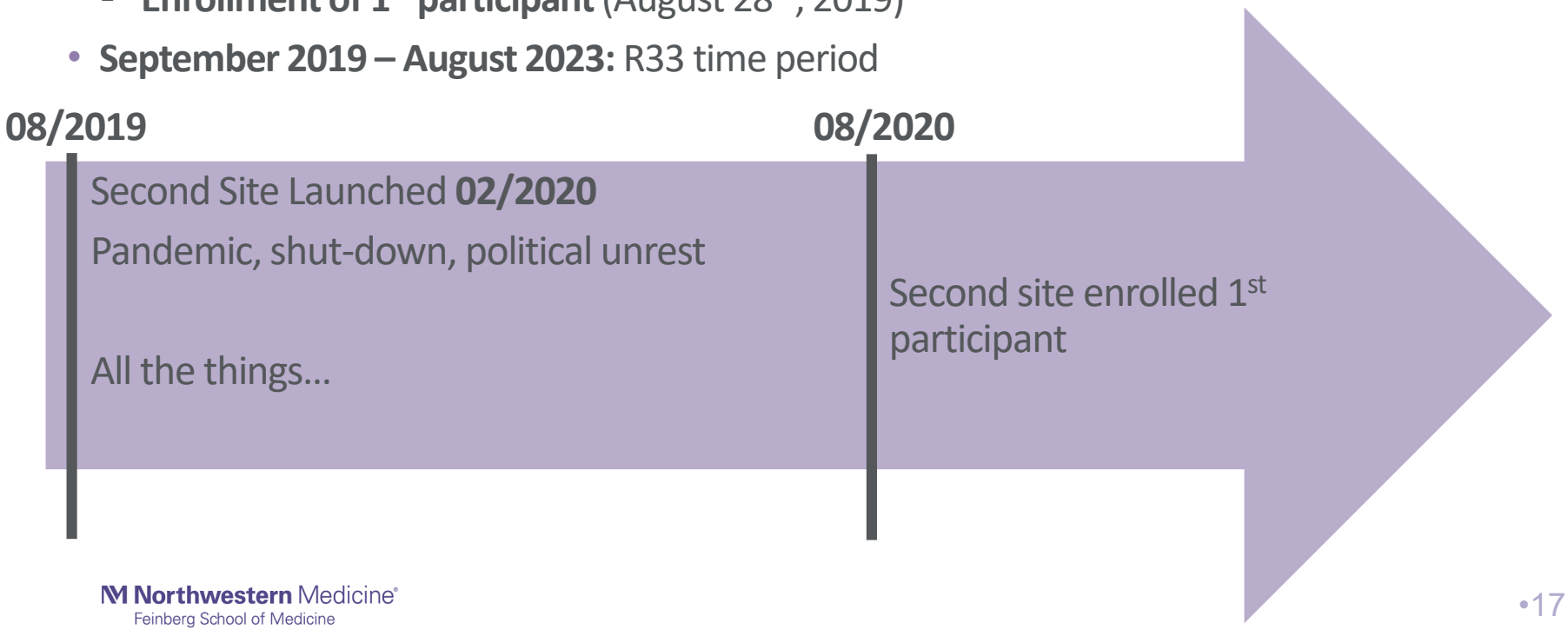
From SAP version 1.0

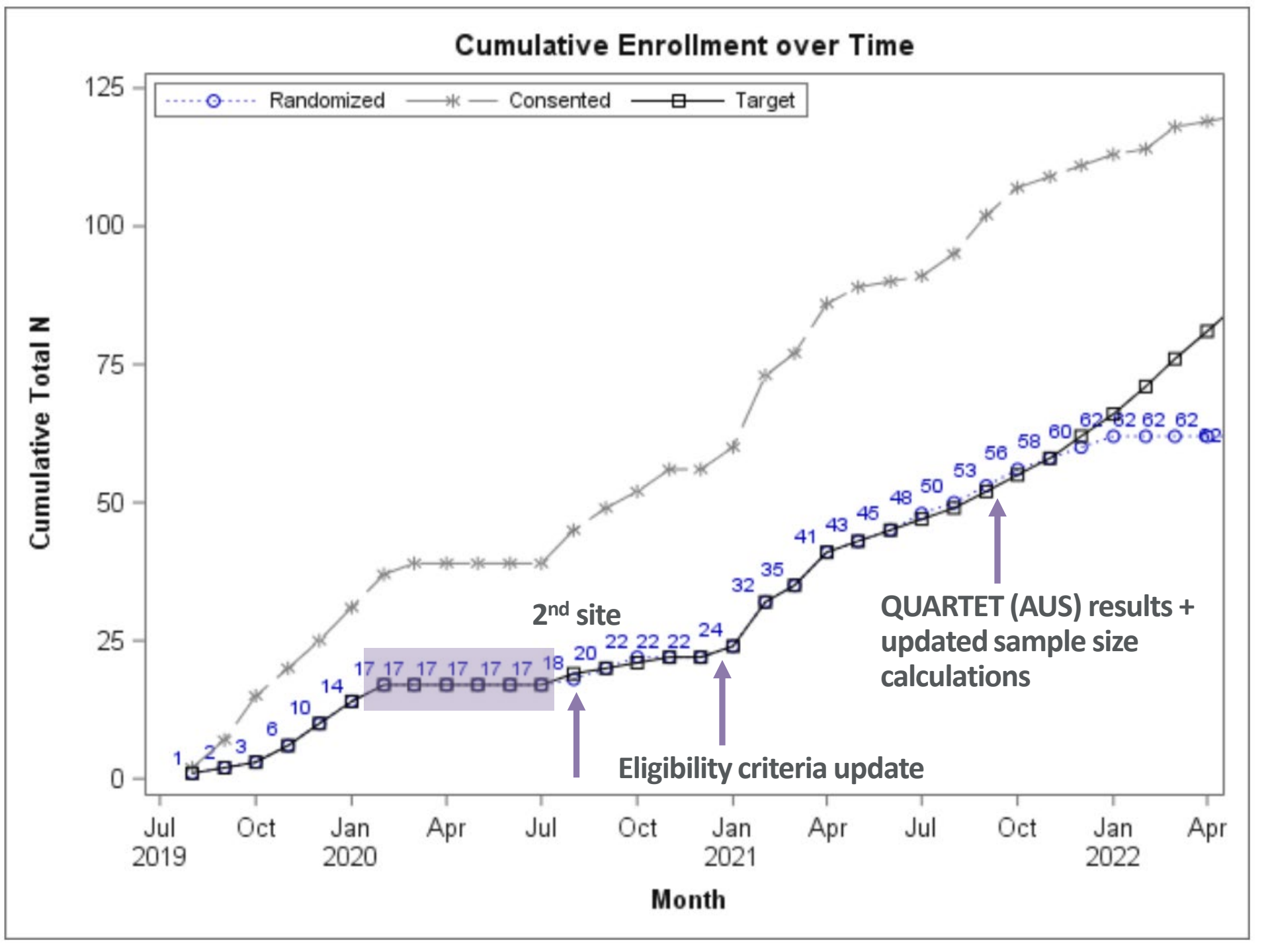
A total of **365 participants will be randomized** (1:1 allocation). We anticipate an analytic sample size of **292 based on 365 participants at randomization and a 20% dropout rate by the 12-week follow-up time point.** We base sample size and power calculations conservatively on an independent two-sample t-test. The analysis methods, ANCOVA, will increase precision on intervention effect when controlling for relevant baseline covariates, thereby providing additional power of detecting intervention effect.

For primary outcome analyses, an independent two-sample t-test **provides 80% power to detect a 5 mmHg difference in SBP between the intervention and comparator arms assuming a two-sided 5% level of significance and a 15 mmHg standard deviation in outcome.** This estimate is based on a 2017 Cochrane systematic review update evaluating the effects of fixed-dose combination therapy and systematic review on quarter dose combination therapy, and a pilot trial of quarter-dose combination therapy [3]. We assume baseline SBP has a moderate correlation with follow-up SBP ($r \approx 0.50\text{-}0.6$); under this assumption, sample size calculations based on ANCOVA has the potential to allow for over 90% power under the same assumptions for remaining parameters.

Back to the timeline – grant/big picture

- **June 2018**: NOA
- <R61 Milestones>
  - Product supply (Sharp); contracts and third-party agreements
  - Protocol and informed consent finalized
  - Management/communication plan; MOP – workflow, recruitment, procedures; Data and Safety Monitoring Plan (DSMP), Data Management Plan (DMP)
  - Regulatory approvals
  - **Enrollment of 1st participant** (August 28th, 2019)
- **September 2019 – August 2023:** R33 time period




Cumulative Enrollment over Time
Randomized
Consented
Target
Cumulative Total N
125
100
75
50
25
0
Jul 2019
Oct
Jan 2020
Apr
Jul
Oct
Jan 2021
Apr
Jul
Oct
Jan 2022
Apr
Month
1 2 3 6 10 14 17 17 17 17 17 17 18 20 22 22 22 24 32 35 41 43 45 48 50 53 56 58 60 62 62 62 62 62
2nd site
Eligibility criteria update
QUARTET (AUS) results + updated sample size calculations

Updates and challenges

- **Second site** to boost recruitment – always easier said than done

- Options to reduce contact during the pandemic:
  - Removed 24-hour ambulatory BP requirement
  - 1-lead EKG
  - Provision of BP monitors to participants
  - Remote options to complete specific study procedures – refer to the '*' here →

Informed consent	X*
Demographics †	X*
Automated office (health center) blood pressure measured in the previous 12 weeks	X*
Blood pressure and heart rate measurements, by research team	X
Electrocardiogram	X ‡
Anthropometrics and medical history	X*
Concomitant medications	X*
Lifestyle questions	X*
PROMIS global health	X*
Laboratory assessments§	X ‡
24-hour ambulatory blood pressure monitor	X
Inclusion and exclusion criteria	X*

Updates and challenges

- Expansion of eligibility criteria around BP

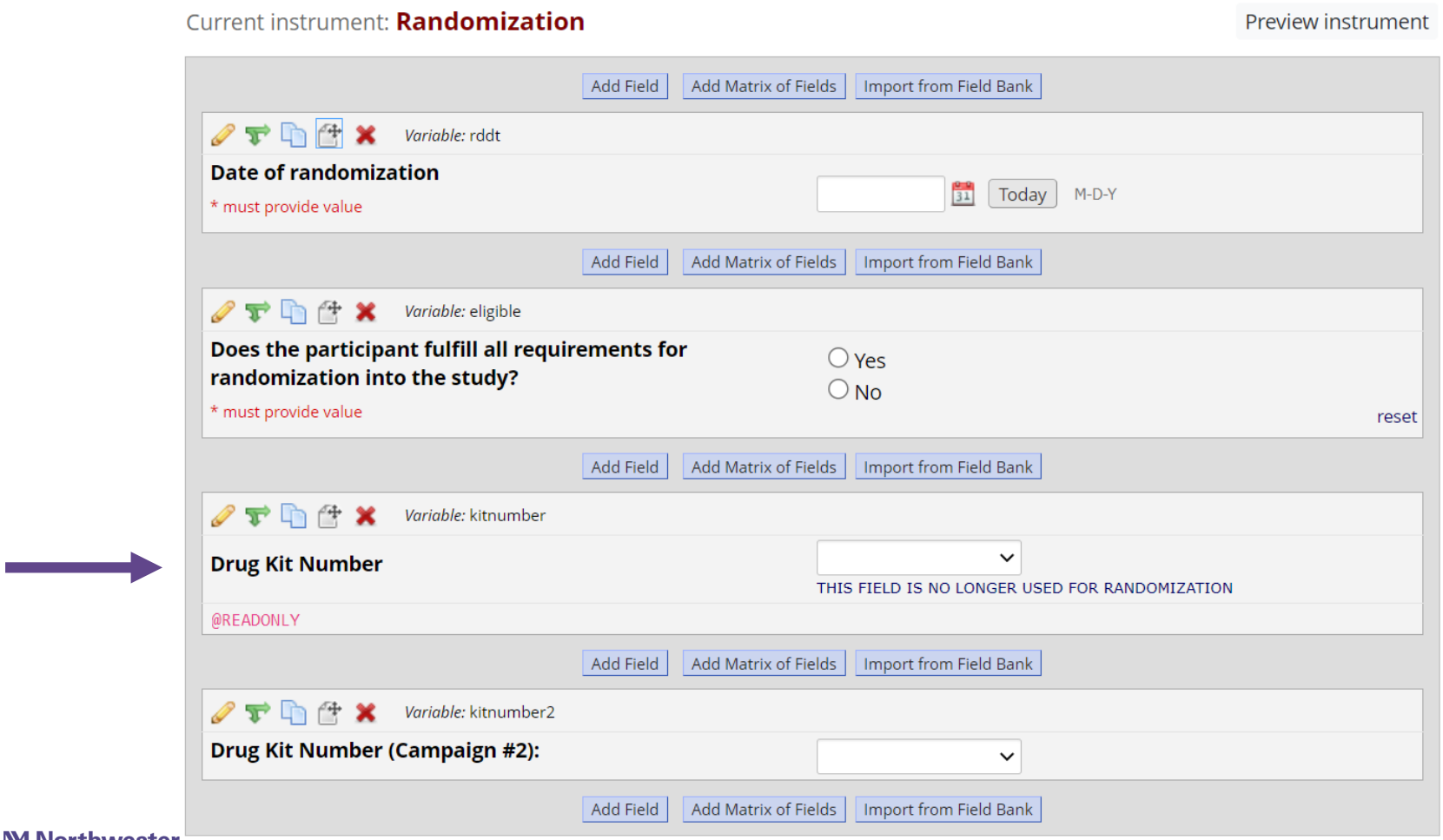
- (understandably) Pressures from funder re: enrollment numbers: continued difficulty in justification for funds for study that is underperforming on recruitment
  - Suggested interim analysis
  - Worked with DSMB to develop an interim analysis plan
  - Updated sample size requirements

- **All of these things carried logistical, operational challenges + required protocol amendments (and all the things that go along with those)**

Randomization Logistics

This is a double-blind study

- The initial randomization tables (one for production and one for development) were imported into the QUARTET USA project (Russo site only)



Randomization Logistics

Maintaining the blind and ensuring drug kits correctly corresponded to the right arm required some additional thought

- Typically, we would code this something like:
  - 0, Arm A
  - 1, Arm B

[study_arm]	Drug ID:	dropdown
		0, Drug A 1, Drug B

- When setting up the randomization module in REDCap, the uploaded randomizations tables would be a random smattering of 0s and 1s (generated by statistical software to ensure equal numbers, etc.)…

This is what is typically uploaded into REDCap (one for development and one for production)

study_arm
0
0
1
1
0
1
…

Randomization Logistics

Maintaining the blind and ensuring drug kits correctly corresponded to the right arm required some additional thought

- Instead, we made our randomization field the “kitnumber” – no longer 0s and 1s…

[kitnumber]	Drug Kit Number *THIS FIELD IS NO LONGER USED FOR RANDOMIZATION*	dropdown
		1492556 | 1492556
		1754916 | 1754916
		1663910 | 1663910
		1944231 | 1944231
		1525094 | 1525094
		1175102 | 1175102
		1842499 | 1842499
		1262338 | 1262338
		1378141 | 1378141

Randomization Logistics

This is a double-blind study

blockID	blockSize	rnum	kitnumber	trt	sequence
1	6	0.492557	1492556		1
1	6	0.754916	1754916		2
1	6	0.66391	1663910	Treatment	3
1	6	0.944232	1944231	IDs here	4
1	6	0.525095	1525094		5
1	6	0.175102	1175102		6

This is what was uploaded into REDCap

Note: when we added a second site, randomization logistics were even more difficult

Adding a Second Site

From the database + randomization perspective

- Since the study was not set up using Data Access Groups (DAGs) within REDCap database, we **cloned** the first site's database

QUARTET USA Study Sites

Site Name	Site Location	REDCap Database	Site Code	Participant IDs
"Russo": Martin T. Russo Family Health Center	245 S Gary Ave Bloomingdale, IL 60108	QUARTET USA	1	1001, 1002, etc.
"Ashland": Ashland Family Health Center	5159 S Ashland Ave Chicago, IL 60609	QUARTET USA - Ashland	3	3001, 3002, etc.

- → Anytime there is an update to one database, we need to ensure that the same update occurs in the other (and also the test database)

- → created issues on back end when merging data

Interim Analysis

Enrollment was slower than we would have hoped

- We were in continued discussion with the funder and the DSMB
- We conducted an unplanned **interim conditional power analysis**
- At the same time, we **updated the analytic plan** to a Linear Mixed Model (LMM), using the **six-week time point in analyses as well**
  - Originally, it was going to be a simpler ANCOVA model – looking at Week 12, controlling for baseline
  - QUARTET (AUS) results also came out at this time – their analytic strategy used an LMM
  - Thus, to make most use of our data AND to align with QUARTET (AUS), we performed an interim analysis using this new analytic strategy

Interim Analysis

In collaboration with the DSMB chair and DSMB statistician

Solution for Fixed Effects: SBP = SBP_baseline + Arm					
Effect	trt	Estimate	Standard Error	DF	t Value
Intercept		63.9718	23.5595	40	2.72
Baseline SBP		0.4771	0.1692	32	2.82
Arm	1	-7.2374	3.4698	32	-2.09
Arm	2	--Reference--			

In the calculation for conditional power (CP), we take this test statistic value and evaluate what power may be if:

1. From here to the end of the study, there is **no trend** (Null assumption).
2. From here to the end of the study, this **current trend** continues (Current trend assumption).
3. From here to the end of the study, the originally hypothesized trend (80% power, 5mmHg difference, etc.) were to hold (**alternative trend** assumption).

We allow the assumed **information fraction** to vary according to different projected recruitment numbers.

Interim Analysis

Recall – our initial sample size called for analytic sample size = 292 (planned to recruit N=364 total!)

Total N	Scenario	CP Estimate
71	Null	0.29
71	**Alternative**	**0.89**
71	**Current Trend**	**0.88**
77	Null	0.27
77	**Alternative**	**0.90**
77	**Current Trend**	**0.90**
84	Null	0.25
84	**Alternative**	**0.90**
84	**Current Trend**	**0.92**
92	Null	0.23
92	Alternative	0.91
92	Current Trend	0.94

Interim Analysis

Our NEW sample size justification

The initial sample size calculations called for a total of 365 participants to be randomized (1:1 allocation). We anticipated an analytic sample size of 292 based on 365 participants at randomization and a 20% dropout rate by the 12-week follow-up time point. We originally based sample size and power calculations conservatively on an independent two-sample t-test.

"Based on results of interim analyses…we updated our recruitment target to 87 participants (1:1 allocation). The **analytic sample size of 77 is anticipated based on 87 participants at randomization and a conservatively estimated 12% dropout rate by the 12-week follow-up time point based on 8% dropout rate observed through September 2021."**

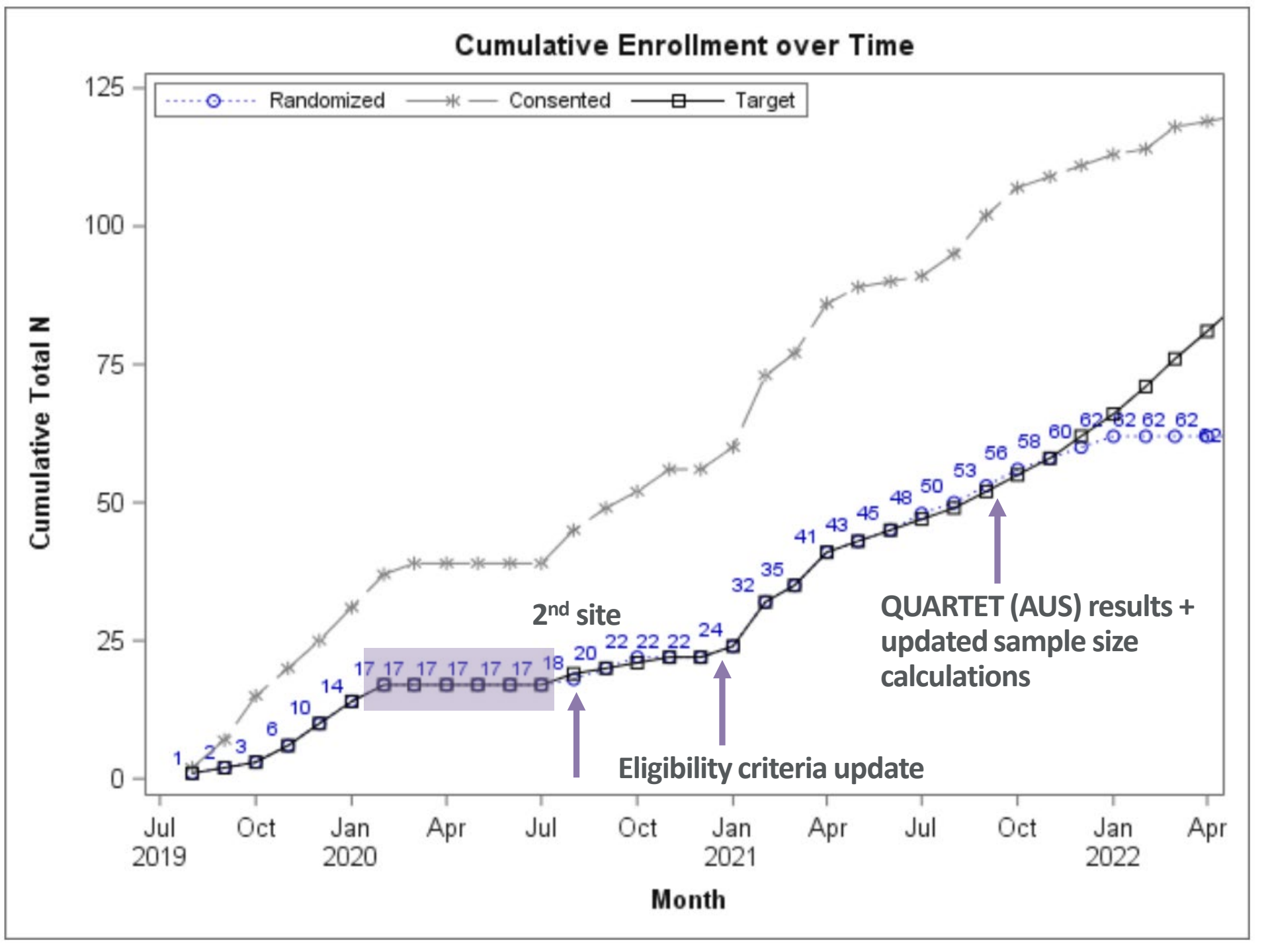
Interim Analysis

Our NEW sample size justification

"…we **conducted an interim conditional power analysis**, taking into consideration information from both the QUARTET USA trial data as of August 2021 and further the QUARTET (Australia) results. These interim analyses, **incorporating information to date**, suggested that a **sample size of at least 77**, and a **12% dropout rate**, would **provide over 90% conditional power** based on a sample of 87 randomized participants."

Note: understandably, the **huge** difference between original (N=364) and the final (N=87) recruitment targets required A LOT of **very careful, detailed but vague** justification

Baldridge, A. S., Huffman, M. D., Lazar, D., Abbas, H., Flowers, F. M., Quintana, A., ... & Ciolino, J. D. (2022). Efficacy and safety of a quadruple ultra-low-dose treatment for hypertension (QUARTET USA): Rationale and design for a randomized controlled trial. *American heart journal*, *254*, 183-193.


Cumulative Enrollment over Time
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1 2 3 6 10 14 17 17 17 17 17 17 18 20 22 22 22 24 32 35 41 43 45 48 50 53 56 58 60 62 62 62 62 62
2nd site
Eligibility criteria update
QUARTET (AUS) results + updated sample size calculations

The decision on stopping the study

...came in collaboration with the funder and DSMB...

- Recruitment continued to be slow
- We ultimately ran out of time as we had agreed to halt the study by **May 2022**, regardless of recruitment numbers
- Now, we are in the process of analyzing the writing up study results
  - Primary results manuscript
  - clinicaltrials.gov updates pending
  - Qualitative analysis pending
  - We will be pooling our data with the Australia study data as well (they had over 600 study participants)

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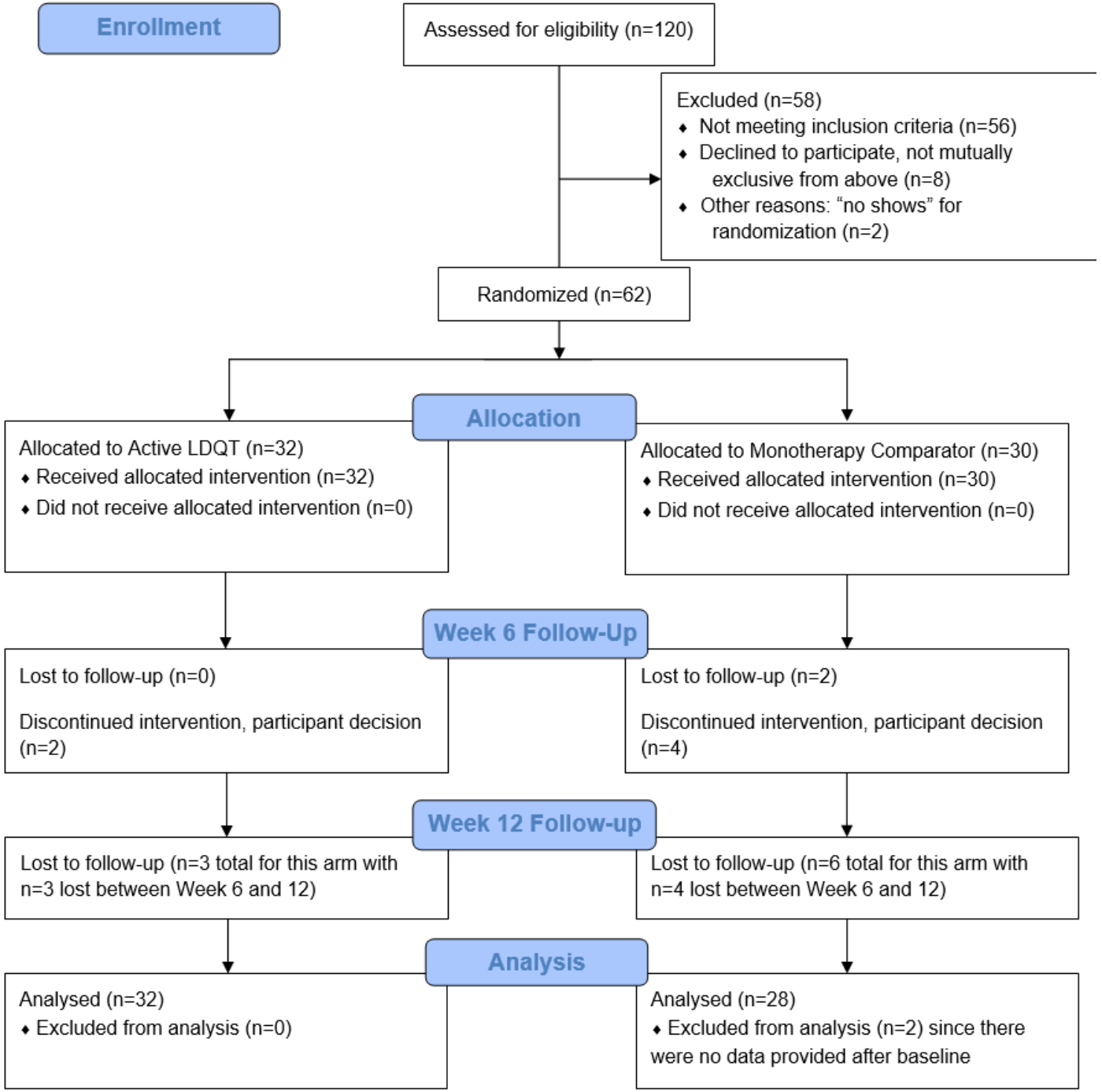
Some Preliminary Results


Enrollment
Assessed for eligibility (n=120)
Excluded (n=58)
♦ Not meeting inclusion criteria (n=56)
♦ Declined to participate, not mutually exclusive from above (n=8)
♦ Other reasons: "no shows" for randomization (n=2)
Randomized (n=62)
Allocation
Allocated to Active LDQT (n=32)
♦ Received allocated intervention (n=32)
♦ Did not receive allocated intervention (n=0)
Allocated to Monotherapy Comparator (n=30)
♦ Received allocated intervention (n=30)
♦ Did not receive allocated intervention (n=0)
Week 6 Follow-Up
Lost to follow-up (n=0)
Discontinued intervention, participant decision (n=2)
Lost to follow-up (n=2)
Discontinued intervention, participant decision (n=4)
Week 12 Follow-up
Lost to follow-up (n=3 total for this arm with n=3 lost between Week 6 and 12)
Lost to follow-up (n=6 total for this arm with n=4 lost between Week 6 and 12)
Analysis
Analysed (n=32)
♦ Excluded from analysis (n=0)
Analysed (n=28)
♦ Excluded from analysis (n=2) since there were no data provided after baseline

Participant Demographics

Variable		Overall (N=62)	Comparator (N=30)	Active (N=32)
Sex	Male	34 (54.84%)	17 (56.67%)	17 (53.13%)
Age	Mean (std), Range	52 (11.52), (26 - 78)	52 (10.52), (34 - 73)	52 (12.55), (26 - 78)
Race/Ethnicity	White/Caucasian/Other	6 (9.68%)	2 (6.67%)	4 (12.50%)
	Black/Sub Saharan African Decent	11 (17.74%)	7 (23.33%)	4 (12.50%)
	Hispanic	**45 (72.58%)**	**21 (70.00%)**	**24 (75.00%)**
Country of Birth	**Mexico**	**34 (54.84%)**	**15 (50.00%)**	**19 (59.38%)**
	USA	21 (33.87%)	12 (40.00%)	9 (28.13%)
	Other	**7 (11.29%)**	**3 (10.00%)**	**4 (12.50%)**
Insurance	Private	5 (8.06%)	4 (13.33%)	1 (3.13%)
	Medicare	6 (9.68%)	3 (10.00%)	3 (9.38%)
	Medicaid	**15 (24.19%)**	**8 (26.67%)**	**7 (21.88%)**
	Medicare & Medicaid	**3 (4.84%)**	**1 (3.33%)**	**2 (6.25%)**
	None	**30 (48.39%)**	**13 (43.33%)**	**17 (53.13%)**
Education	< Grade 9	15 (24.19%)	8 (26.67%)	7 (21.88%)
	Grade 9-11	10 (16.13%)	4 (13.33%)	6 (18.75%)
	High school/GED	22 (35.48%)	9 (30.00%)	13 (40.63%)
	Undergraduate/AA degree	12 (19.35%)	7 (23.33%)	5 (15.63%)
	Technical/vocational	3 (4.84%)	2 (6.67%)	1 (3.13%)
Household Income	**$1-$25,000 per year**	**34 (54.84%)**	**15 (50.00%)**	**19 (59.38%)**
	$25,001-$50,000 per year	16 (25.81%)	8 (26.67%)	8 (25.00%)
	$50,001-$75,000 per year	2 (3.23%)	2 (6.67%)	0 (0.00%)
	No income	**6 (9.68%)**	**2 (6.67%)**	**4 (12.50%)**
	Choose not to answer	4 (6.45%)	3 (10.00%)	1 (3.13%)

Participant Baseline Characteristics

Variable	Overall (N=62)	Comparator (N=30)	Active (N=32)
BMI	34 (7.34), (23 - 53)	34 (7.89), (24 - 53)	33 (6.87), (23 - 48)
Currently on monotherapy	52 (83.87%)	25 (83.33%)	27 (84.38%)
Self-Reported Hypertension Diagnosis	50 (80.65%)	27 (90.00%)	23 (71.88%)
History of Diabetes	17 (27.42%)	7 (23.33%)	10 (31.25%)
History of Depression	16 (25.81%)	9 (30.00%)	7 (21.88%)
History of Smoking	20 (32.26%)	9 (30.00%)	11 (34.38%)
Weekly Alcohol Use	19 (30.65%)	9 (30.00%)	10 (31.25%)

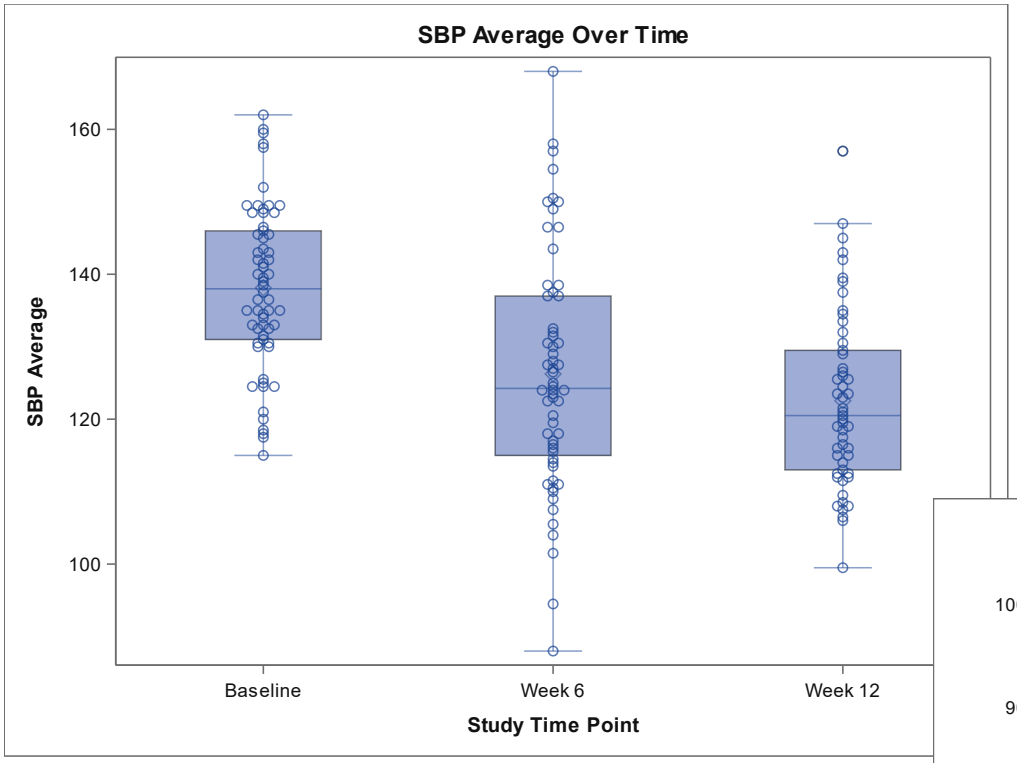
Blood Pressure Descriptive Statistics

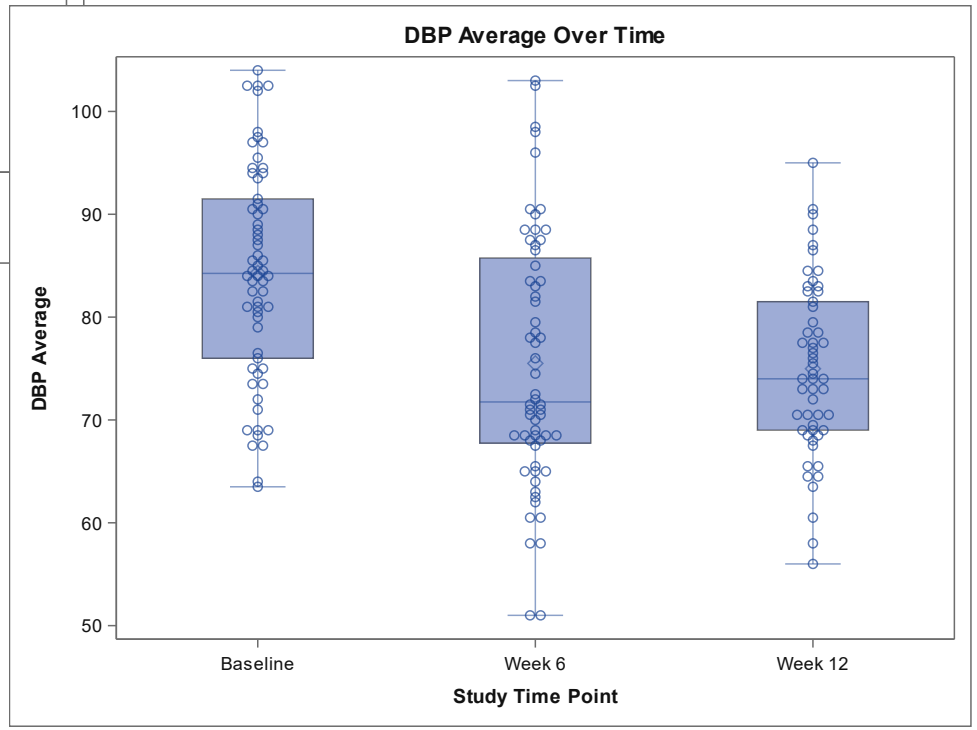
		Baseline		Week 6		Week 12	
		Comparator	Active	Comparator	Active	Comparator	Active
SBP (mmHg)	Mean	138.68	137.59	130.09	122.88	124.21	121.17
	Std	10.75	11.78	18.78	13.14	12.60	11.86
DBP (mmHg)	Mean	84.28	84.31	78.86	72.56	77.02	73.29
	Std	11.54	9.57	14.23	9.77	7.72	8.95

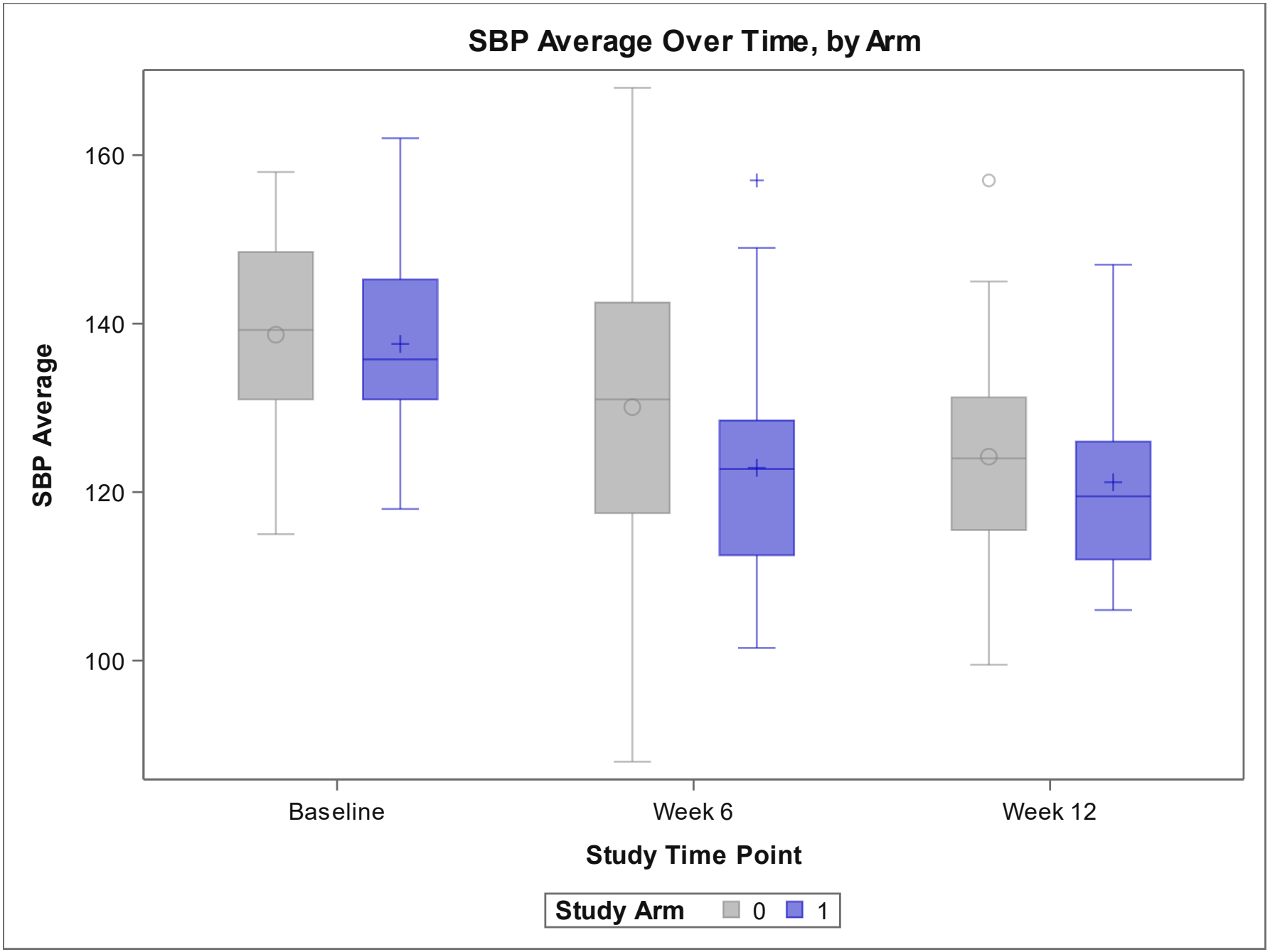
BP Control:

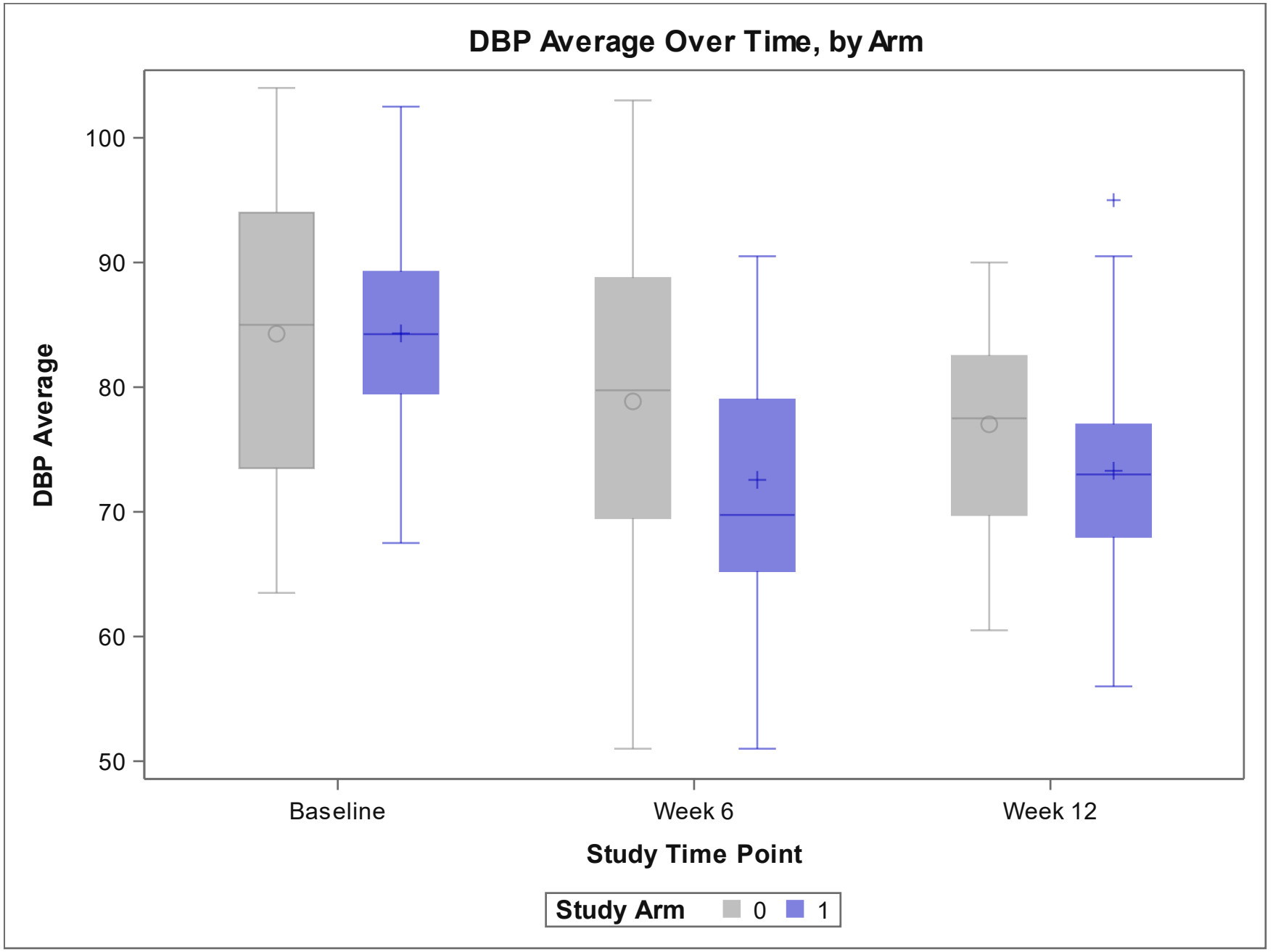
- Week 6: 69% in active vs. 39% in comparator
- Week 12: 67% in active vs. 58% in comparator

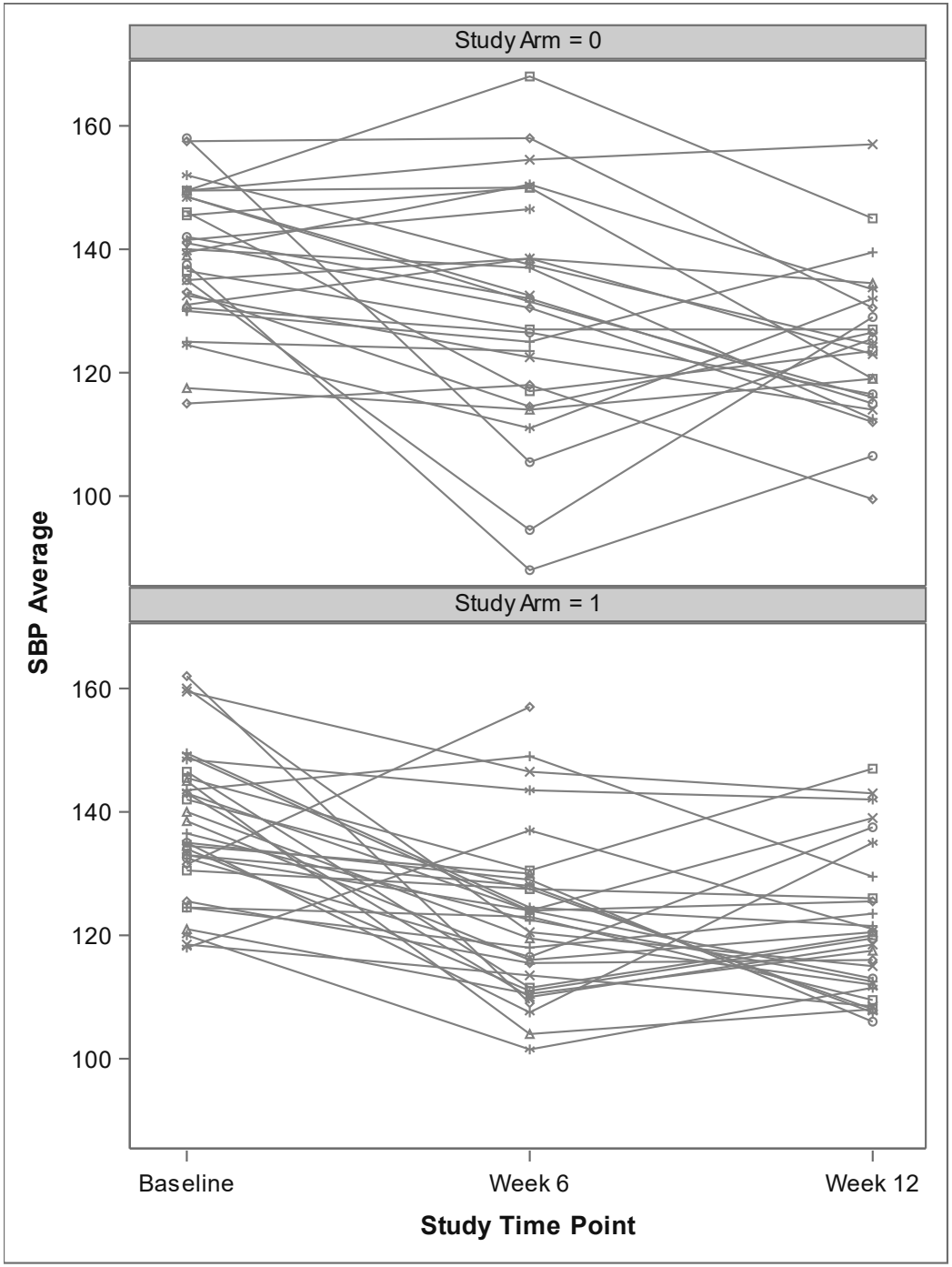
Overall Distributions

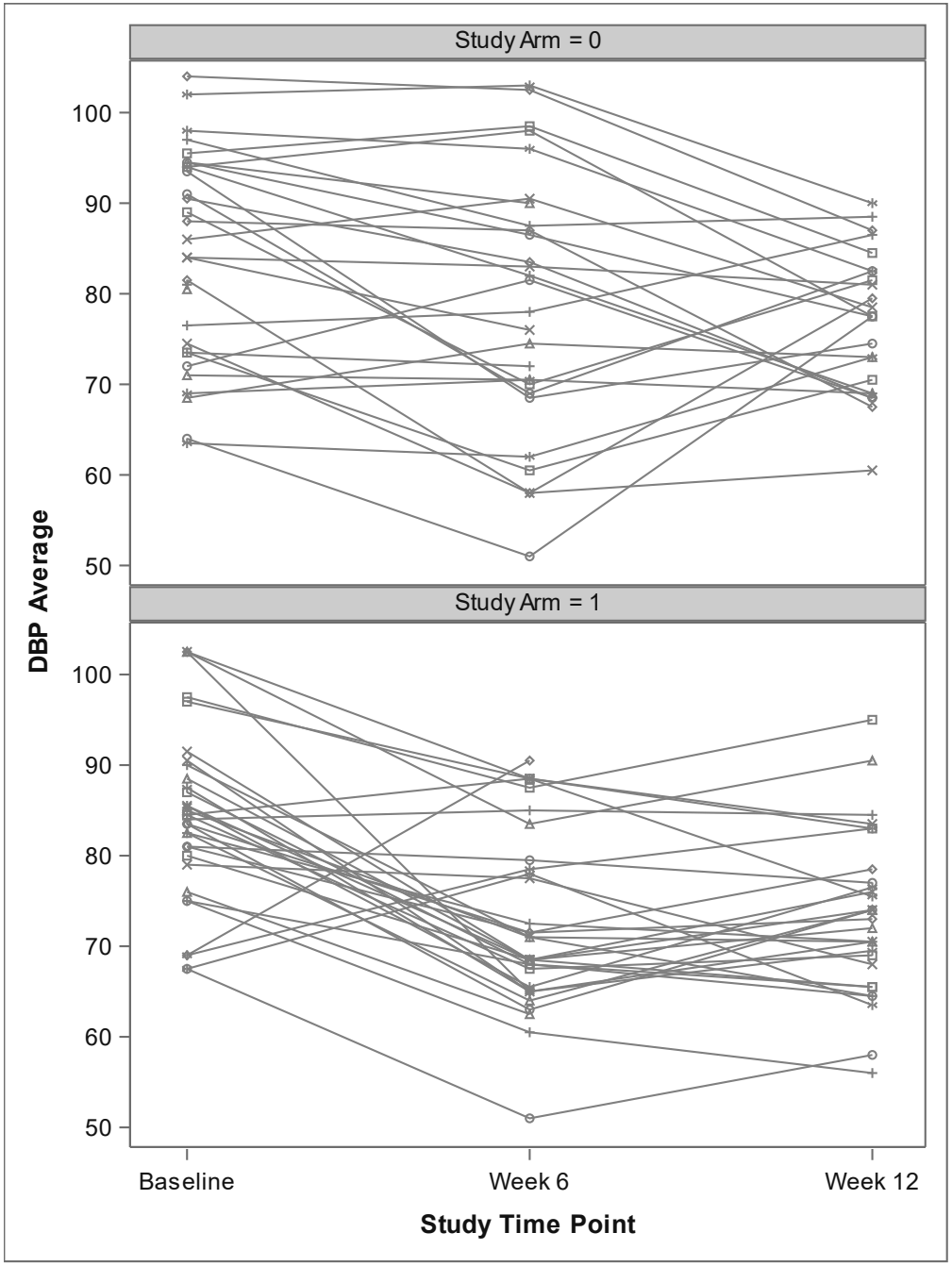





SBP Average Over Time, by Arm
SBP Average
160
140
120
100
Baseline
Week 6
Week 12
Study Time Point
Study Arm
0
1


DBP Average Over Time, by Arm
DBP Average
100
90
80
70
60
50
Baseline
Week 6
Week 12
Study Time Point
Study Arm
0
1


Study Arm = 0
Study Arm = 1
SBP Average
160
140
120
100
Baseline
Week 6
Week 12
Study Time Point


Study Arm = 0
Study Arm = 1
DBP Average
100
90
80
70
60
50
Baseline
Week 6
Week 12
Study Time Point

Analysis Model Results

SBP

- Model-estimated difference: **-4.78 mmHg** (95% CI: -10.74,1.18 mmHg, p=0.114)
- Adjusted model (for pre-specified covariates of interest) suggest comparable results

DBP

- Model-estimated difference: **-4.86 mmHg** (95% CI: -8.62,-1.11 mmHg, p=0.012)
- Adjusted model (for pre-specified covariates of interest) suggest comparable results

Additional Outcomes

- Modeling **Odds of BP control**:
  - OR (active vs. comparator): **2.40** (0.91,6.34; p=0.077)
  - Adjusted model comparable
- Modeling **Odds of Add-on treatment**:
  - OR: **0.13** (0.03,0.48; p=0.0026)
  - Similar results in adjusted models
- **Adherence** (defined as at least 80% of pills taken)
  - Not significantly different across arms
  - This is true in both adjusted and unadjusted models
  - Also holds true when we analyze # pills taken

	Comparator		Active		Overall	
	N	%	N	%	N	%
Any AE Experienced	14	46.67	20	62.50	34	54.84
Adherent per Protocol	21	70.00	21	65.63	42	67.74
Received Add-on Treatment	16	53.33	6	18.75	22	35.48

Safety Outcomes

	Comparator n=30	Active n=32
Serious adverse event	0 (0)	2 (6.3)*
Any adverse event	14 (46.7)	20 (62.5)
Any adverse event, at least possibly related	3 (10.0)	8 (25.0)
Adverse event leading to discontinuation	8 (26.7)	2 (6.3)

*Both SAEs were deemed unrelated to study medication: 1 was related to a car accident and the other occurred when the participant was NOT taking study medication

Takeaways

In this double-blind, randomized, phase II study…

- Initiating a four-drug, quarter-dose combination blood pressure lowering therapy was associated a **-4.8/-4.9 mmHg** greater reduction in mean change in BP from baseline to 12 weeks compared with standard-dose ARB monotherapy in patients with mild to moderate hypertension.

- **Differences in SBP were not statistically significant**, which we speculate is due to limited power related to the sample size.

- **Adverse events were more common in the intervention arm**, but the rates of discontinuation were higher in the comparator arm. No SAEs were deemed related to the study drug.

Takeaways

- New approaches are needed to achieve lower BP targets, especially for patients and communities with a high burden of hypertension and hypertension-related diseases.
- QUARTET USA was the first trial of four-drug, ultra-low dose blood pressure combination therapy in the US.
- The **direction and magnitude of blood pressure lowering effect was similar between QUARTET(AUS) and QUARTET USA**, despite different study populations, thus strengthening the case for this new approach.

Acknowledgments

- **QUARTET USA** patients, study team members, and **DSMB** members (Paul Muntner [chair], Emily Anderson, Perla Herrera, Ken Jamerson, Chris Lindsell)

- **Northwestern**: Mark Huffman (MPI), Jody Ciolino (MPI), Abi Baldridge, Namratha Kandula, Sadiya Khan, Don Lloyd-Jones, Steve Persell, Jay Paparello

- **Access Community Health Network:** Dani Lazar, Jairo Mejia, Hiba Abbas, Fallon Flowers, Adriana Quintana, Patricia Helbin, Edgar Pizarro

- **University of Sydney:** Clara Chow

- **The George Institute for Global Health/UNSW:** Anthony Rodgers, Emily Atkins, Bruce Neal, Anushka Patel, MA Salam

- **Sponsors:** NHLBI (R33HL139852), NUCATS (U01TR003528), Northwestern

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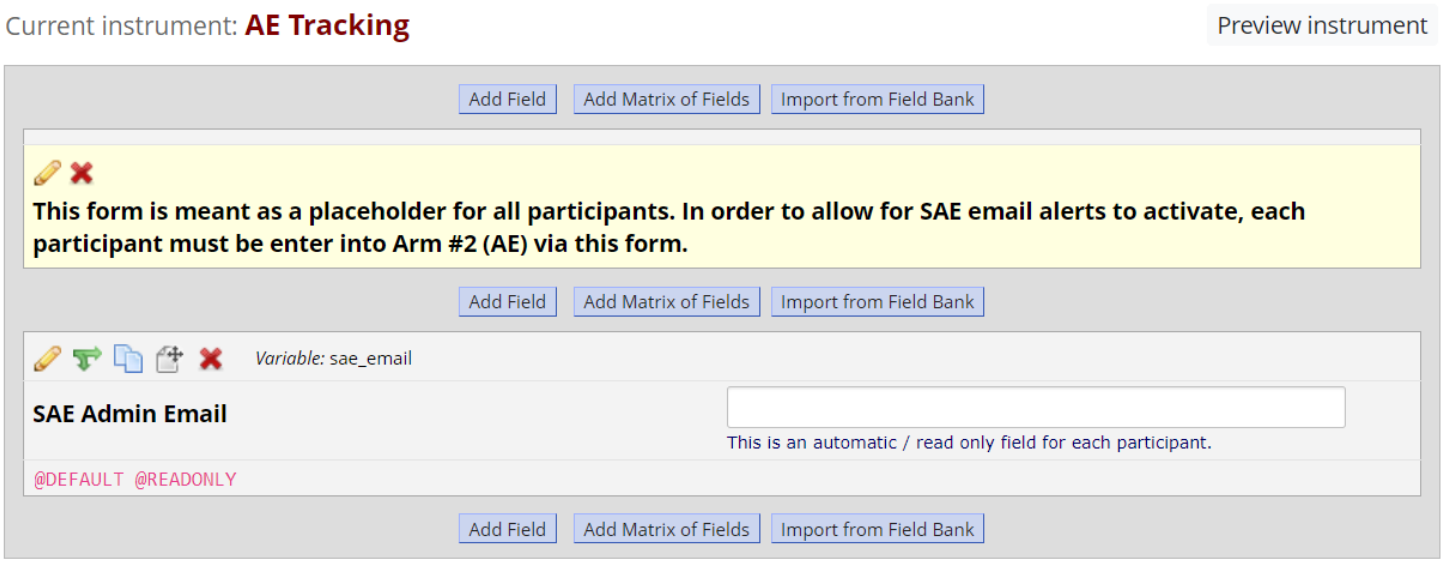
Additional Slides for Reference/Discussion as Needed

Notes on Safety Monitoring / Adverse Events

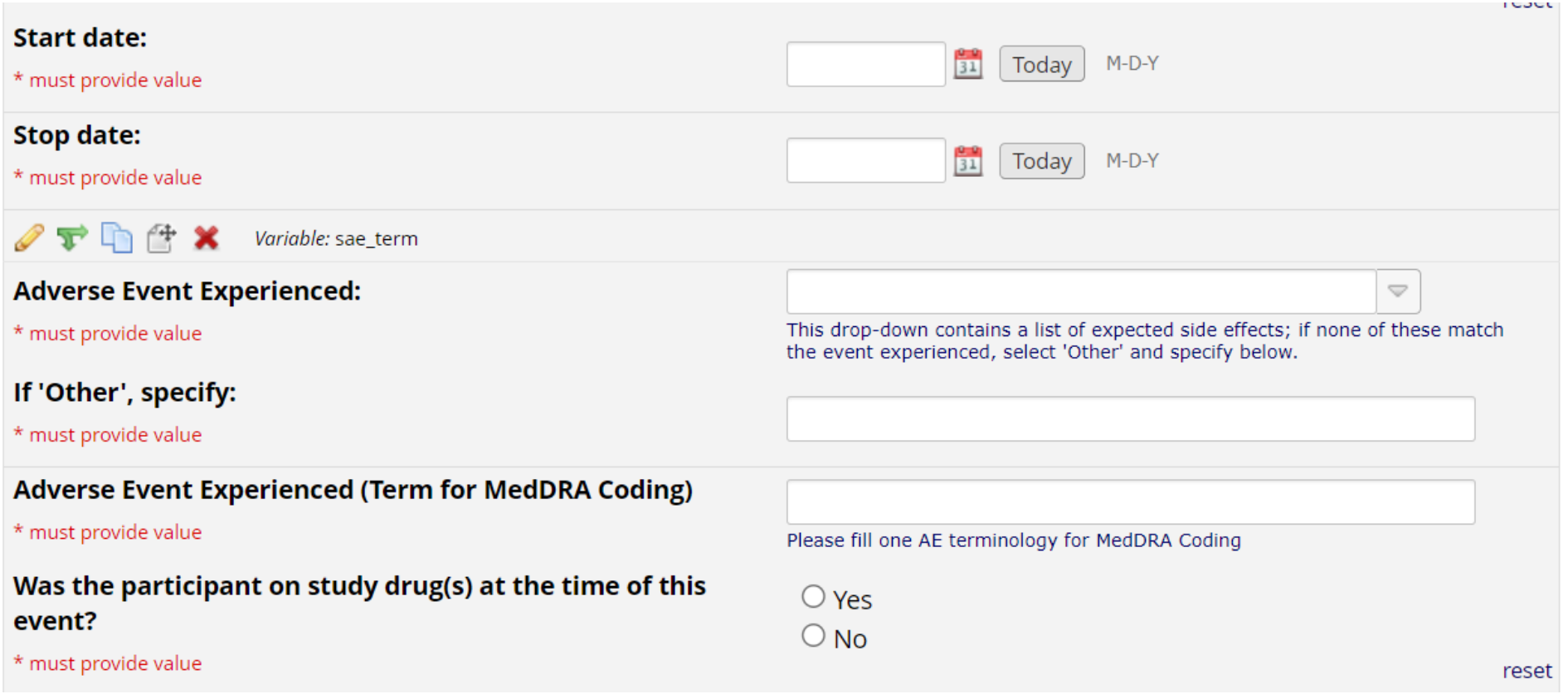
- Sadiya Khan – safety monitor (blinded)
  - Received AE listings on a monthly basis and gave assessment on relatedness and severity
  - Automatic email trigger for SAEs
- AEs solicited via dropdown + open text field
  - AEs of interest = those in side effect profile of study drug(s)
  - Open text field used for 'other' specifications
  - Additional space for narrative
- MedDRA coding via George Clinical (used REDCap)

Notes on Safety Monitoring / Adverse Events



AE Tracking	✓														
Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SAE Alert (survey)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

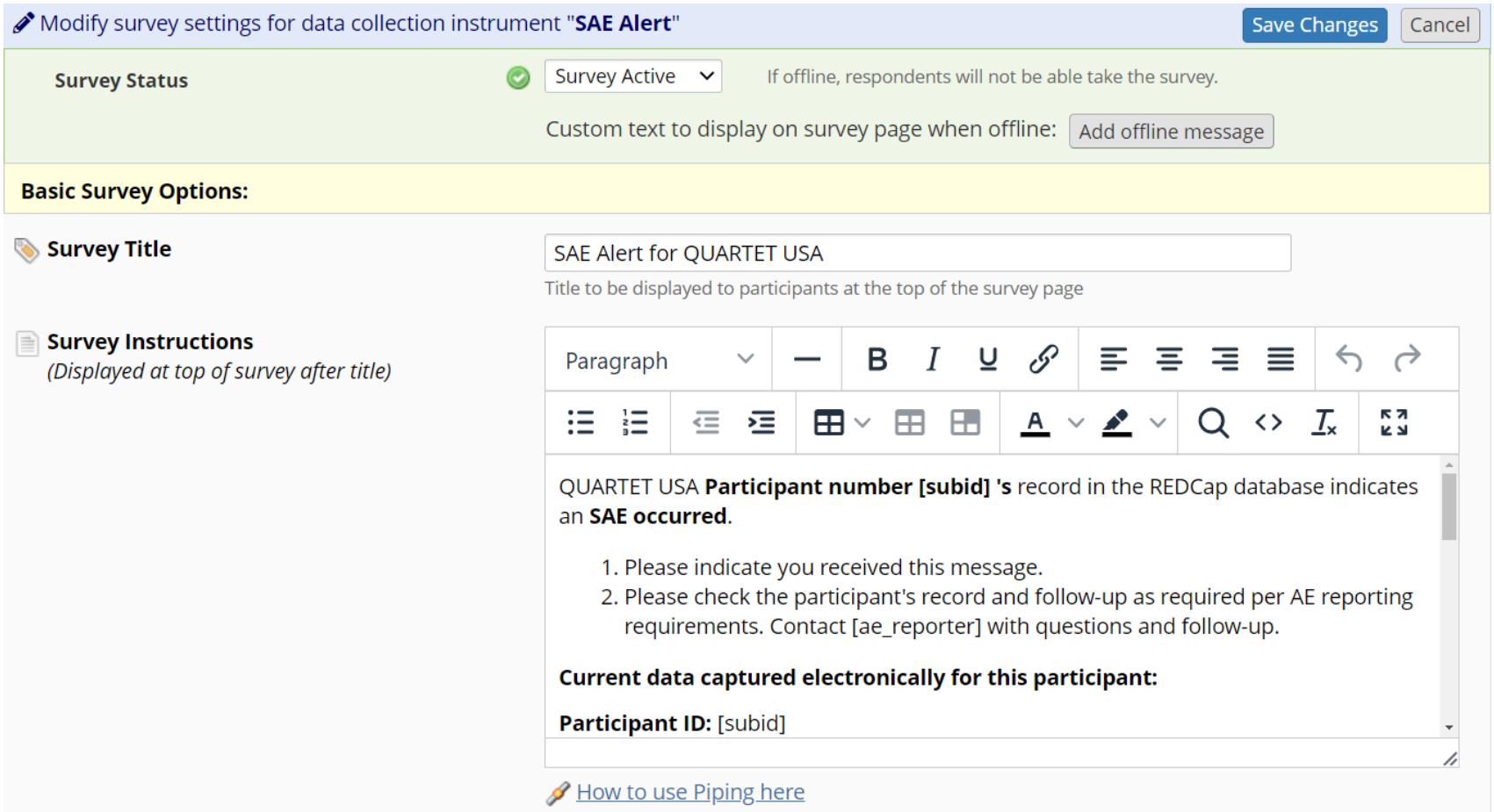
Notes on Safety Monitoring / Adverse Events



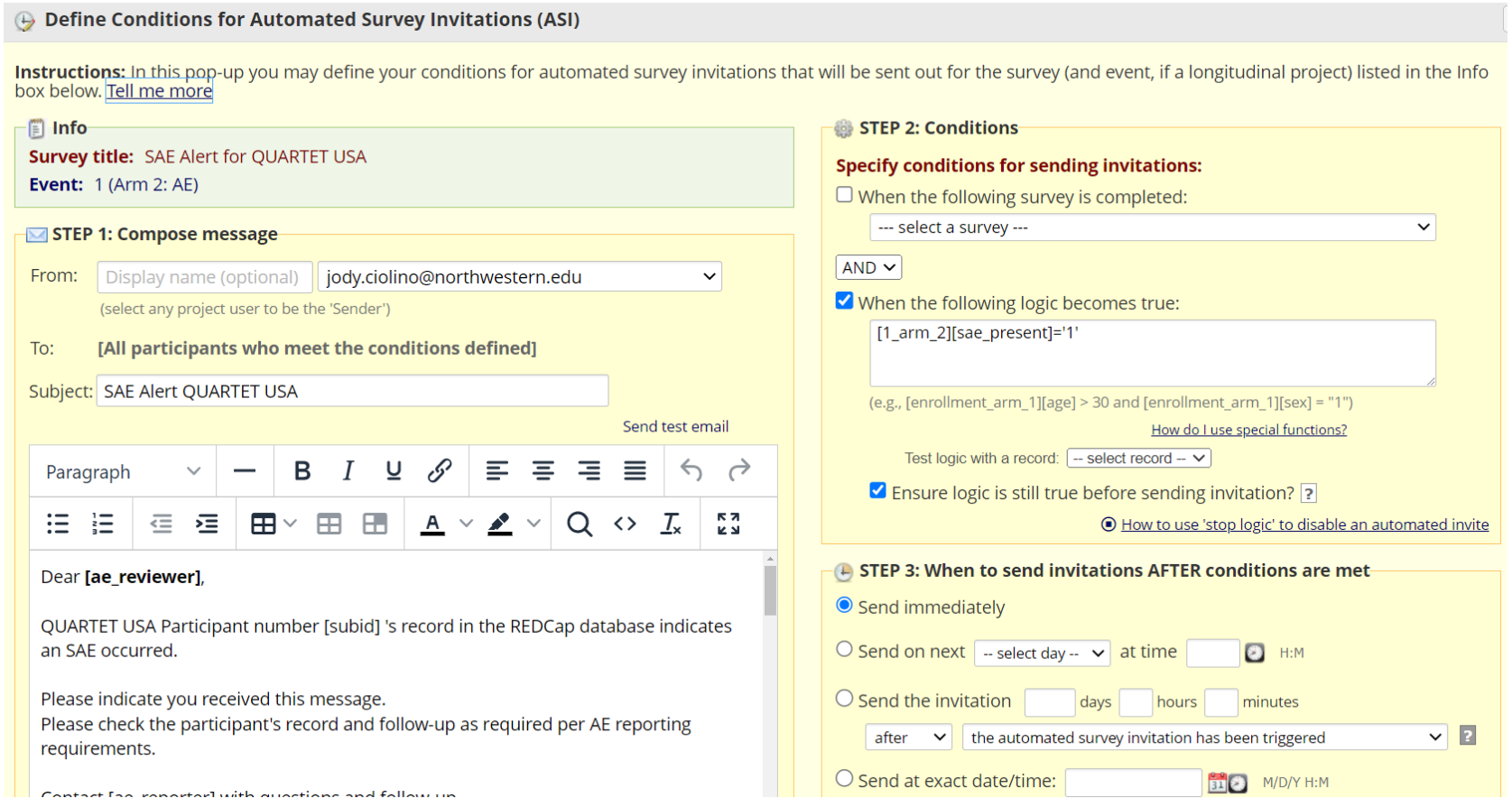
Serious Adverse Event (SAE) Determination

	No	Yes	
Death * must provide value	○	○	reset
Life threatening * must provide value	○	○	reset
Required hospitalization / prolongation of existing hospitalization * must provide value	○	○	reset
Resulted in persistent disability * must provide value	○	○	reset
Resulted in congenital anomaly / birth defect * must provide value	○	○	reset
Important medical event that may require intervention to prevent one of the above * must provide value	○	○	reset
SAE Present:		[ ] View equation This is a calculated field; it will be '1' if an SAE is present and '0' if it is not.	
THIS EVENT MEETS CRITERIA FOR AN SAE.			

Notes on Safety Monitoring / Adverse Events



Notes on Safety Monitoring / Adverse Events



Adding a Second Site

From the database + randomization perspective

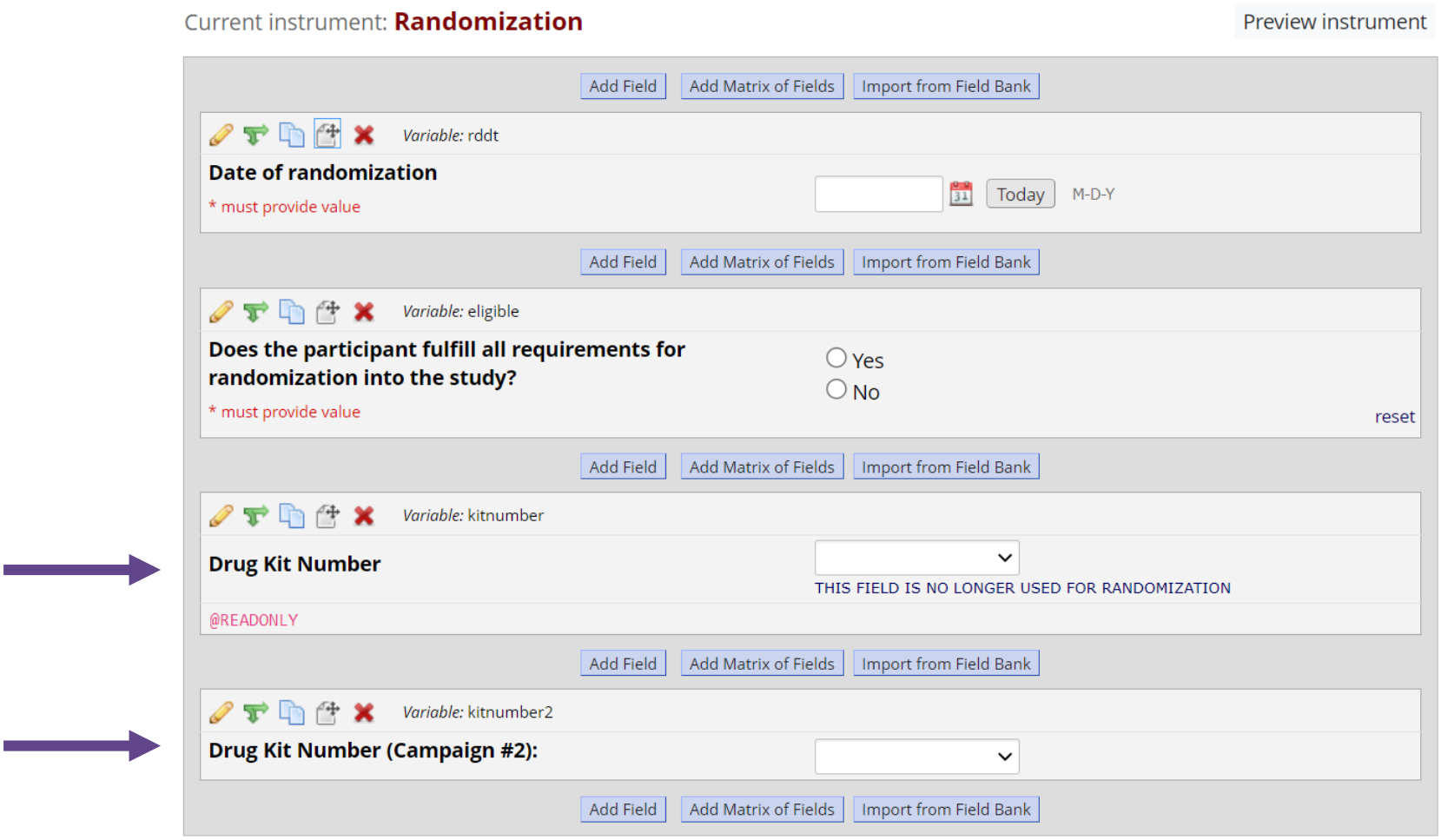
- The first manufacturing campaign from Sharp (our manufacturer) included 120 kits (60 per arm)
- In February of 2020, we opened a second study site (Ashland) with a corresponding database
  - The first kit # at Ashland was: 1949764 – this corresponded to randomization sequence #63 in the original output file
  - **We included 58 kit numbers in the initial randomization table upload to Ashland, up to sequence #120**
  - → this means that the kitnumbers for Ashland initially included the bottom "half" of that initial .csv file we uploaded for the first site (Russo)
- The randomization in the Russo database was untouched at this point, **noting that if we approach either drug expiration dates OR total of 63 randomization at Russo, we would need to update!**

Manufacturing Campaign #2

+ the second site = a HUGE headache with respect to randomization logistics

- April of 2021: second manufacturing campaign drug kits because the existing kits were expiring at each of the study sites
- **Ashland site**: sequences received include #121-#202, this corresponds to 41 kits of active study drug and 41 kits of the compactor (82 kits total were received)
- **Russo site**: sequences received include #203-#399
- There were **less kits of candesartan (comparator) received than planned** → some sequences were NOT used / included in the second shipment
- → **created a "kitnumber2" field** in each database
- The previous randomization model was erased (with the assistance and backup of REDCap administrative support at NU)
- We made the previous "kitnumber" field "read only" using field annotation

…it was really complicated…



Follow-up Discussions

Dear Mark and Jody

The proposed drop in the sample size is unusually large in my experience and I want to reassure senior NHLBI leadership that I understand the rationale for this change. Can you share with me what assumptions in the new power calculation changed to support this lower sample size without unblinding me to unmasked current results? I attached your current protocol, the power calculation is on page 18 bottom. If I understand their assumptions, you projected difference of 5 mm in the BP delta and 15 mm standard deviation and correlation of 0.5 to 0.6 between baseline and final BP measurements. The size of the delta that you discussed with me on reflection does not seem larger to justify such a large decrease in the sample size. I assume that both are still masked.

Interim analysis consisted of conditional power calculations under multiple scenarios. The original power and sample size estimates were based on very conservative assumptions, but this strategy allows us to use the whole of the information from the actual trial data to date, removing some of the 'restrictions' of these previous assumptions.

The conditional power calculation proceeded as follows:

1. In order to capitalize on both the 6-week and 12-week follow-up time points, we calculated an interim test statistic based on a mixed model for follow-up SBP with random participant effect and fixed arm effect. Note this is a slightly different, but a more efficient use of the data than the original model on 12-week SBP alone called for.
2. We used this test statistic and the number of participants to date (the information fraction) to calculate conditional power under varying scenarios. The scenarios included multiple, feasible assumptions on…
    a. trend (e.g., under the originally hypothesized trend of 5mmHg, assuming there was no effect/trend), and
    b. the total information (or sample size) that we may anticipate…ranging from an additional 10 to an additional 150 participants.
3. A little more explanation of conditional power: conditional power = probability of a significant effect once we have all information *given* the current test statistic, the current N, and the assumption on trend. That is, there are less granular assumptions on things like standard deviation, correlations, etc. The assumptions rely on information to date and expected information from here on out.
4. The DSMB reviewed the estimated conditional power under these varying scenarios. Under multiple scenarios on trend, the added 30 participants would provide 90% estimated conditional power.