College of Pharmacy | Beyond the Script

Beyond Study Design and Primary Outcomes: Lessons Learned from a Deprescribing Trial to Increase Cognitive Reserve

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Disclosures

I have no relevant commercial relationships to disclose.

IN*tervention for* ***C****ognitive* ***R****eserve* ***E****nhancement in delaying the onset of* ***A****lzheimer's* ***S****ymptomatic* ***E****xpression* (INCREASE) study was supported by NIA grant # R01AG054130

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Presentation Outline

1. An overview of the INCREASE study design
2. Preliminary findings
3. A closer look at our intervention
4. Dealing with the unexpected
5. Lessons learned

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INCREASE: The Big Picture

Modifiable (~ 40%)

- Cardio-vascular risk factors
- Diet and exercise level
- Depression
- Medications

Non-modifiable (~ 60%)

- Age
- Biological sex
- Race/Ethnicity
- Genetics

Adapted from Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission
https://doi.org/10.1016/S0140-6736(20)30367-6

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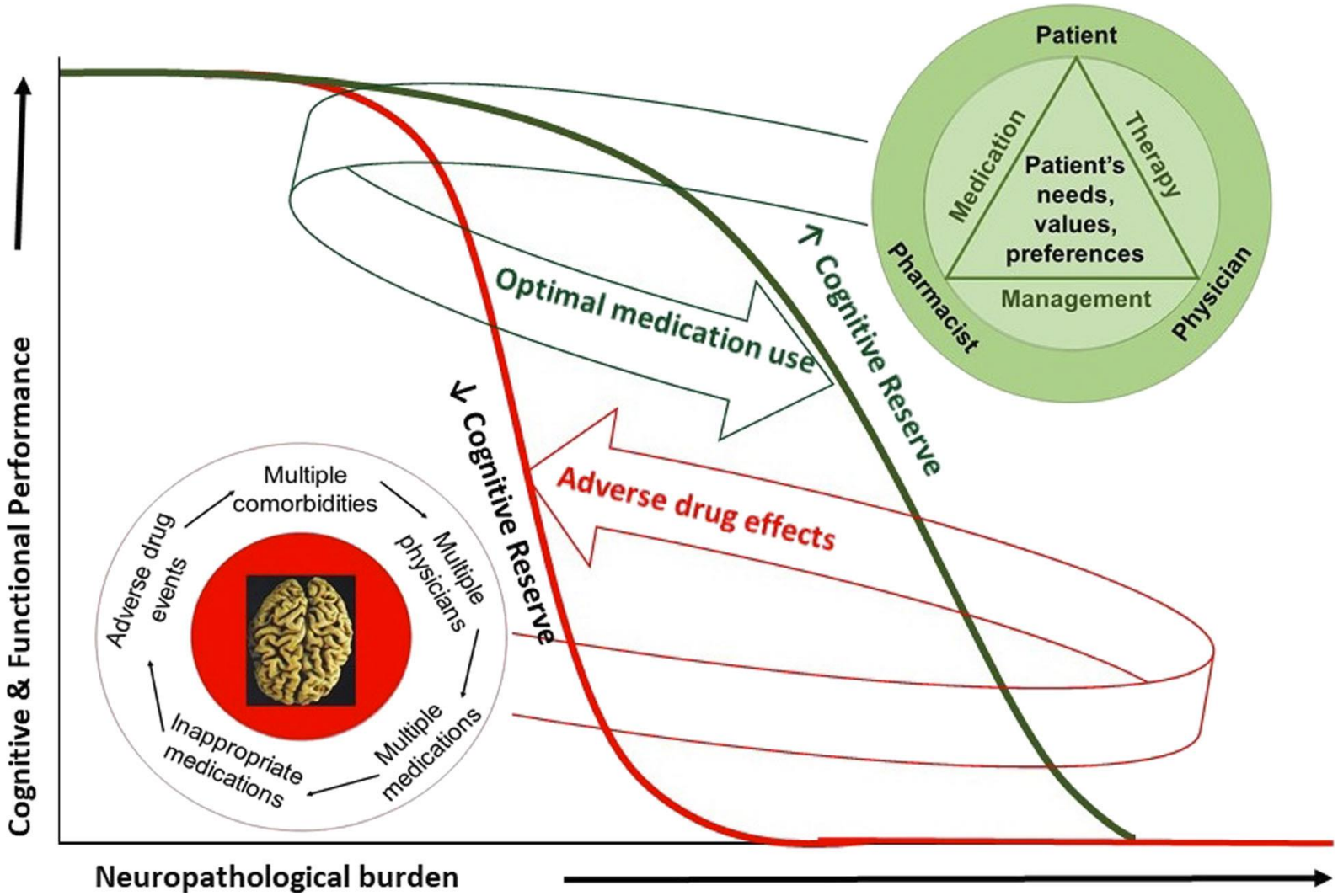
INCREASE: Hypothesis



DC. Moga.et al. INtervention for Cognitive Reserve Enhancement in delaying the onset of Alzheimer's Symptomatic Expression (INCREASE), a randomized controlled trial: rationale, study design, and protocol. Trials. 2019 Dec 30;20(1):806

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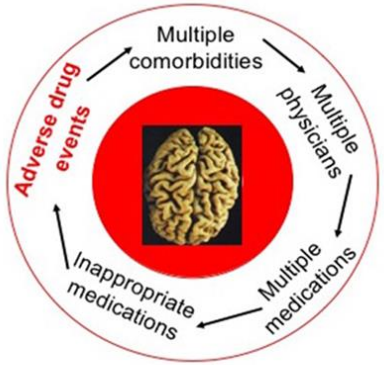
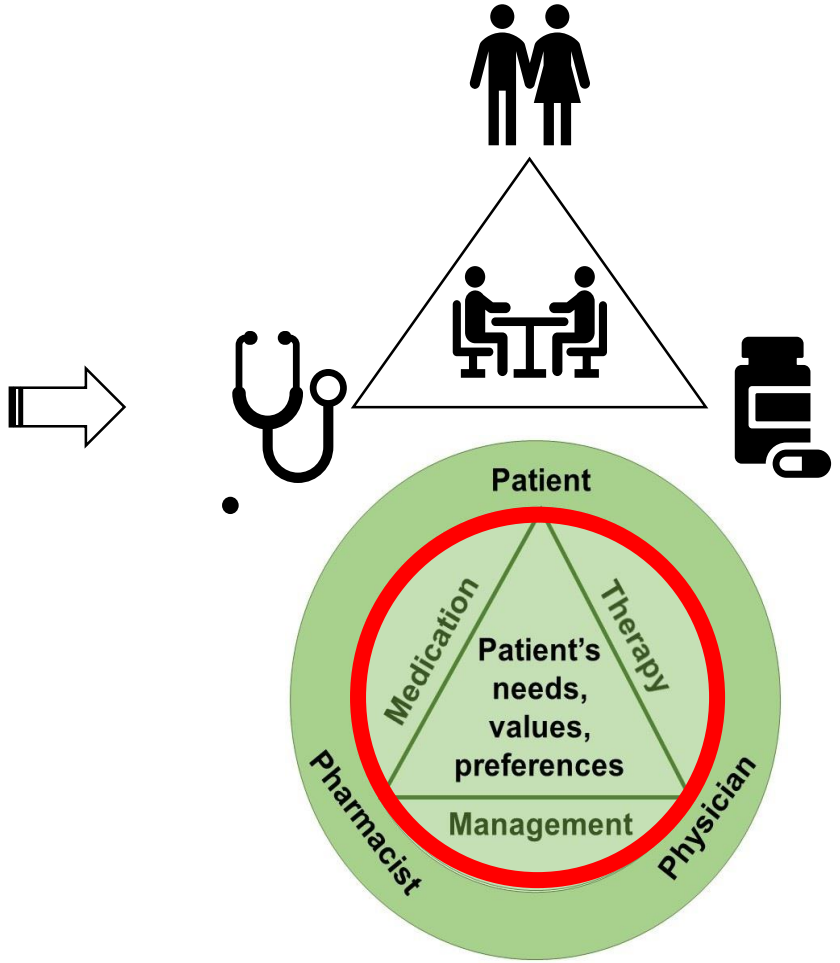
INCREASE: Approach





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INCREASE: Aims & Objectives

Aim 1

Conduct a 12-month, randomized trial to evaluate the impact of our patient-centered, pharmacist-physician team intervention in reducing unnecessary and inappropriate medication use in community-dwelling, elderly, non-demented participants.

1. Assess the effectiveness of the intervention in reducing inappropriate medication use over the study period as determined by the medication appropriateness index (MAI).
2. Investigate the association of β-amyloid positron emission tomography (Aβ-PET) and MAI with cognitive reserve, operationalized as CRCS = scopolamine challenged cognitive test performance versus unchallenged performance.
3. Investigate the effects of the intervention and changes in MAI on CRCS in participants that are Aβ-PET positive or negative over the one-year study period.

Aim 2

Evaluate the impact of preclinical amyloid burden on cognitive reserve deficits and decline to evaluate efficacy of delaying symptomatic disease progression.

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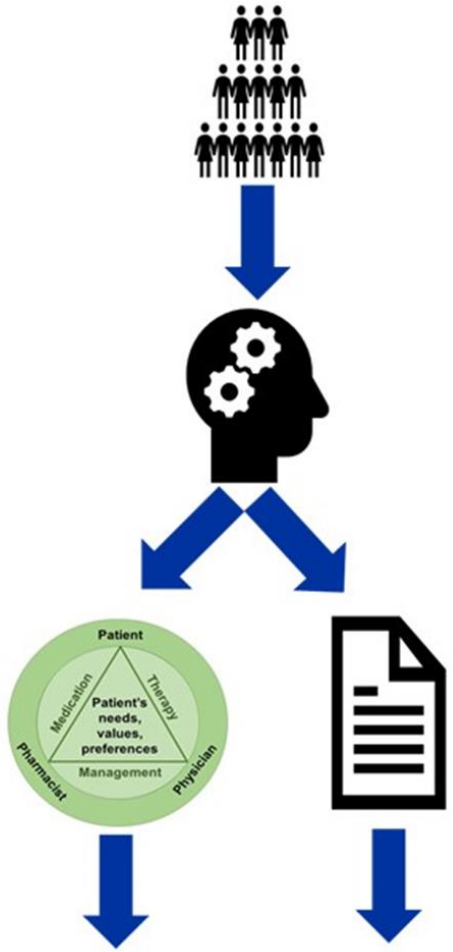
INCREASE: Study Design



Screening: eligibility criteria
- Normal cognition
- ≥ 65 years
- ≥ 1 medication from Beers' 2015 criteria of potentially inappropriate medications

Baseline: Evaluation
- Comorbidities, medication use
- Medication Appropriateness Index
- Cognitive testing: TMTB, MoCA, CVLT (scopolamine challenged, unchallenged)
- Perceived health status (SF-36)

Baseline: Randomization
- PET scan → SUVr for Aβ

Baseline: Intervention
- Stratified randomization by Aβ
- Intervention arm: Patient-centered Medication Therapy
- Control arm (Placebo): education materials

Follow-Up
- 3, 9 months: phone call (updating medication list)
- 6 months: in-person visit (cognitive testing, intervention)

End of Study:
- Medication Appropriateness Index
- Cognitive testing: TMTB, MoCA, CVLT (scopolamine challenged, unchallenged)
- Perceived health status (SF-36)

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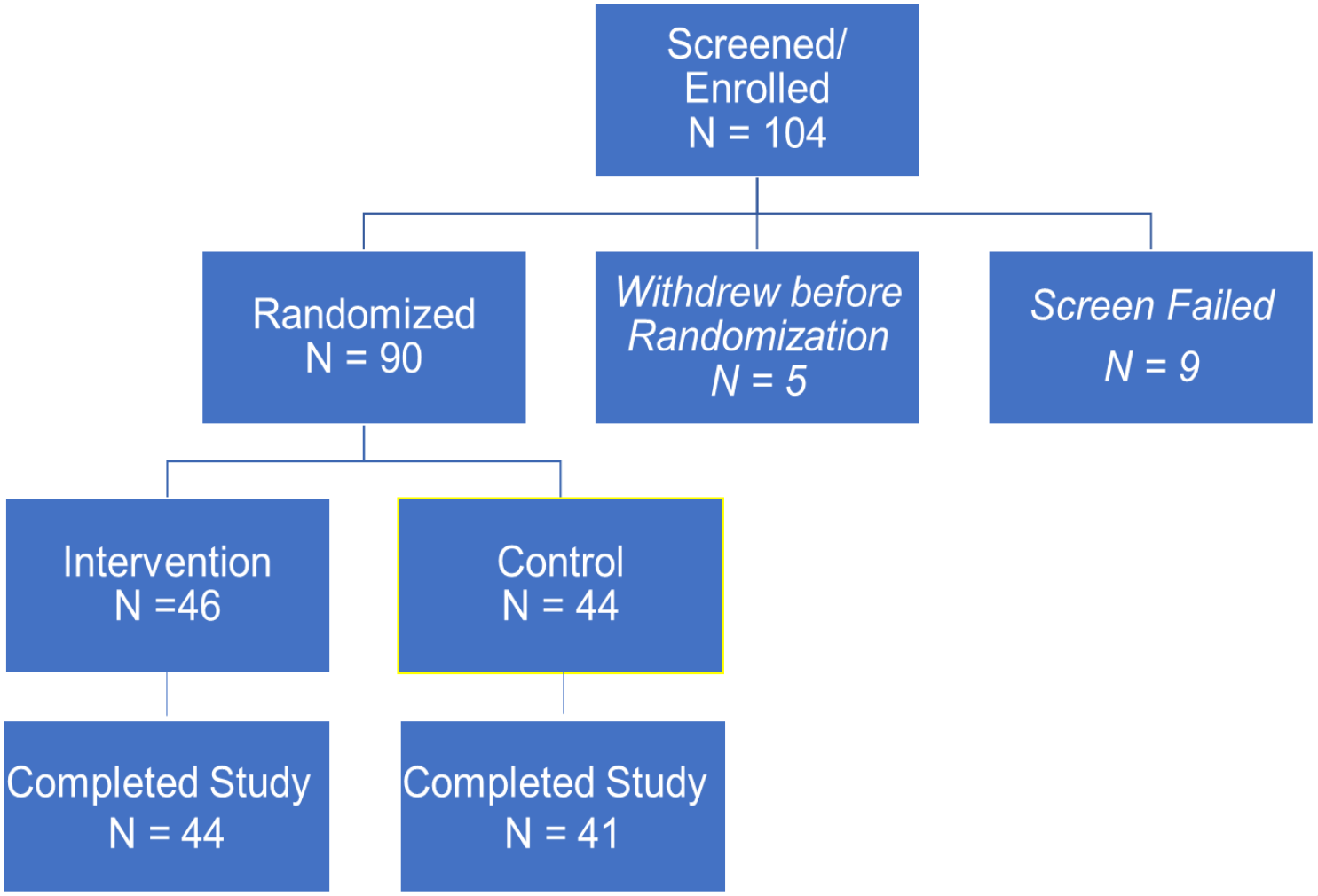
INCREASE: Results



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Characteristic at enrollment		INCREASE (N=90)	Control (n=44)	Intervention (n=46)
Age	Mean (SD)	73.9 (6.0)	74.1 (6.6)	73.4 (5.6)
	Median (Min-Max)	73.5 (65-93)	73 (69-93)	72 (65-87)
Sex	Female, N	57	23	34
Ethnicity	Not Hispanic or Latino, N	90	44	46
Race	American Indian/Alaskan Native, N	0	0	0
	Asian, N	2	2	0
	Black/African American, N	8	2	6
	White, N	80	40	40
Years of education	Mean (SD)	16.5 (2.8)	16.4 (2.6)	16.5 (3.0)
SUVr	≥1.4, N	29	14	15
Total medications	Mean (SD)	12.8 (4.8)	12.9 (4.8)	12.7 (5.0)
Beers' list medications	Mean (SD)	2.4 (1.2)	2.2 (1.2)	2.5 (1.2)
MAI	Mean (SD)	12.1 (8.5)	10.6 (7.4)	13.5 (9.4)
TMTB (in seconds)	Mean (SD)	104.7 (57.5)	101.8 (60.9)	107.4 (54.7)
TMTB z-score	Mean (SD)	-0.29 (1.1)	-0.23 (1.2)	-0.34 (1.1)

SUVr: Standardized Uptake Value ratio; MAI: Medication Appropriateness Index; TMTB: Trail Making Test B;

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Aim 1

Outcome (mean ± sem)	End of Study		Mean difference	p-value
	Control	Intervention		
MAI[1]	11.2±0.6	9.4±0.6	1.80±0.82	0.029
TMTB challenged conditions[2]	95.2±7.0	88.6±7.3	-6.6±10.0	0.51
TMTB z-score challenged conditions[3]	-0.10±0.14	0.03±0.14	0.13±0.20	0.51

[1] model adjusted for age, sex, education, baseline MAI, # baseline meds, # baseline Beers' list meds, SUVr≥1.4
[2] model adjusted for age, sex, education, baseline challenged TMTB, NAART, baseline MAI, SUVr≥1.4
[3] model adjusted for age, sex, education, baseline challenged TMTB z-score, NAART, baseline MAI, SUVr≥1.4

sem: standard error of the mean; MAI: Medication Appropriateness Index; TMTB: Trail Making Test B; NAART: North American Adult Reading Test

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Aim 2

Outcome (mean ± sem)	SUVr	End of Study		Mean difference	p-value tx effect
		Control	Intervention		
MAI[1]	≥ 1.4	11.99±1.08	9.14±1.01	2.86±1.49	0.05
	< 1.4	10.74±0.68	9.40±0.72	1.34±0.98	0.17
TMTB challenged conditions[2]	≥ 1.4	106.9±9.8	74.4±9.2	-31.5±13.5	0.02
	< 1.4	92.7±5.9	87.4±6.3	-5.3±8.6	0.54
TMTB z-score challenged conditions[3]	≥ 1.4	-0.64±0.27	0.23±0.25	-0.87±0.37	0.017
	< 1.4	0.11±0.16	-0.07±0.17	-0.18±0.23	0.45

All models include amyloid*tx interaction term and main effects
[1] model adjusted for age, sex, education, baseline MAI, # baseline meds, # baseline Beers' list meds
[2] model adjusted for age, sex, education, NAART, baseline challenged TMTB, baseline MAI
[3] model adjusted for age, sex, education, NAART, baseline challenged TMTB z-score, baseline MAI

sem: standard error of the mean; MAI: Medication Appropriateness Index; TMTB: trail making test B; NAART: North American Adult Reading Test

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Adverse Events

N=248 total AE were reported, of which N=17 (6.9%) SAE

- N=2 deaths
- N=11 hospitalizations
- N=2 injurious falls
- N=1 car accident
- N=1 emergency room visit without hospitalization

- No serious adverse events related to study procedures
- No falls related to administration of scopolamine
- No evidence that MTM increased risks of AE

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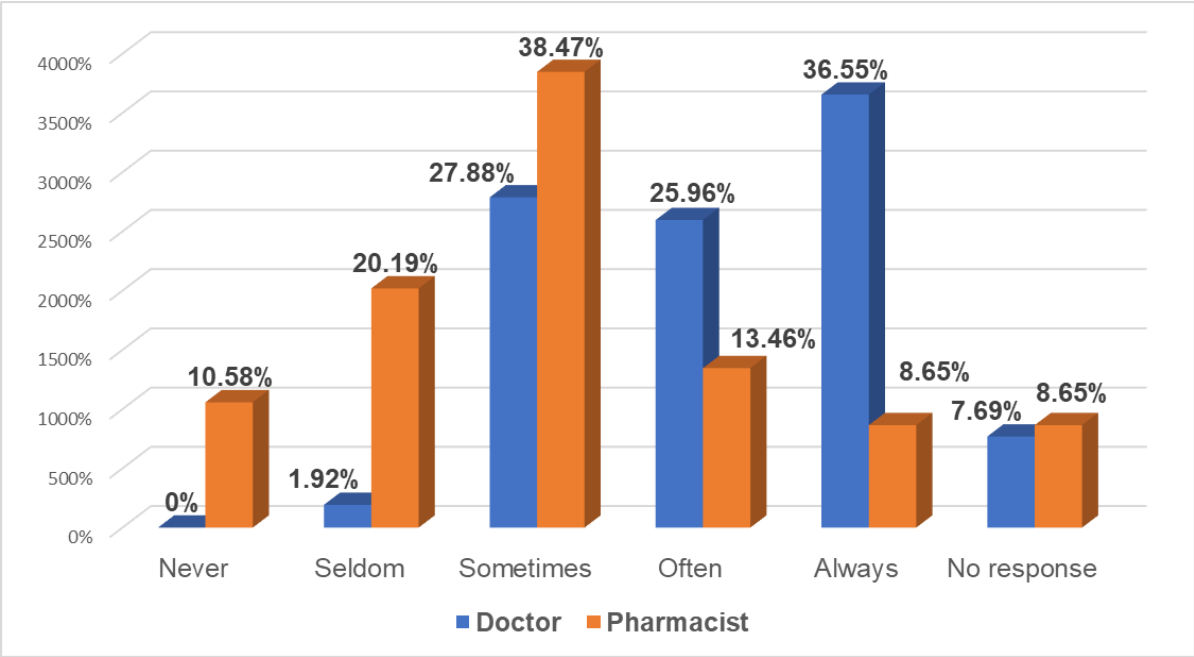
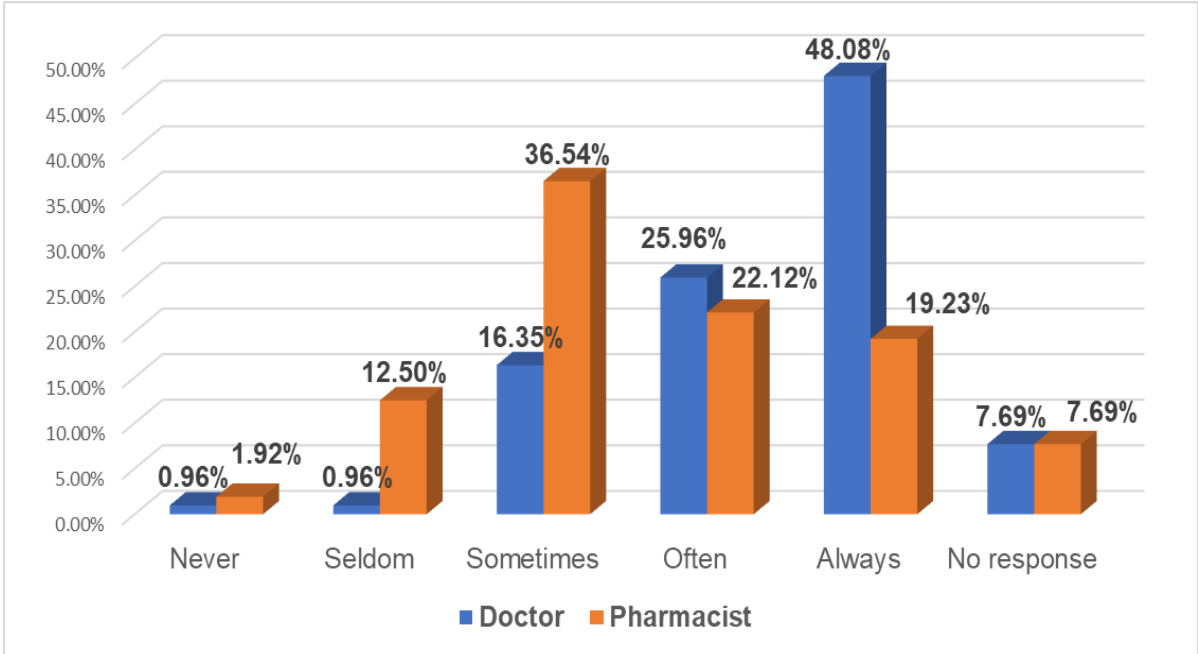
INCREASE: Getting into the weeds…

I talk to my doctor/pharmacist about the medications I am taking



If I have a question about a medication I am taking, I would reach out to ask my doctor/pharmacist



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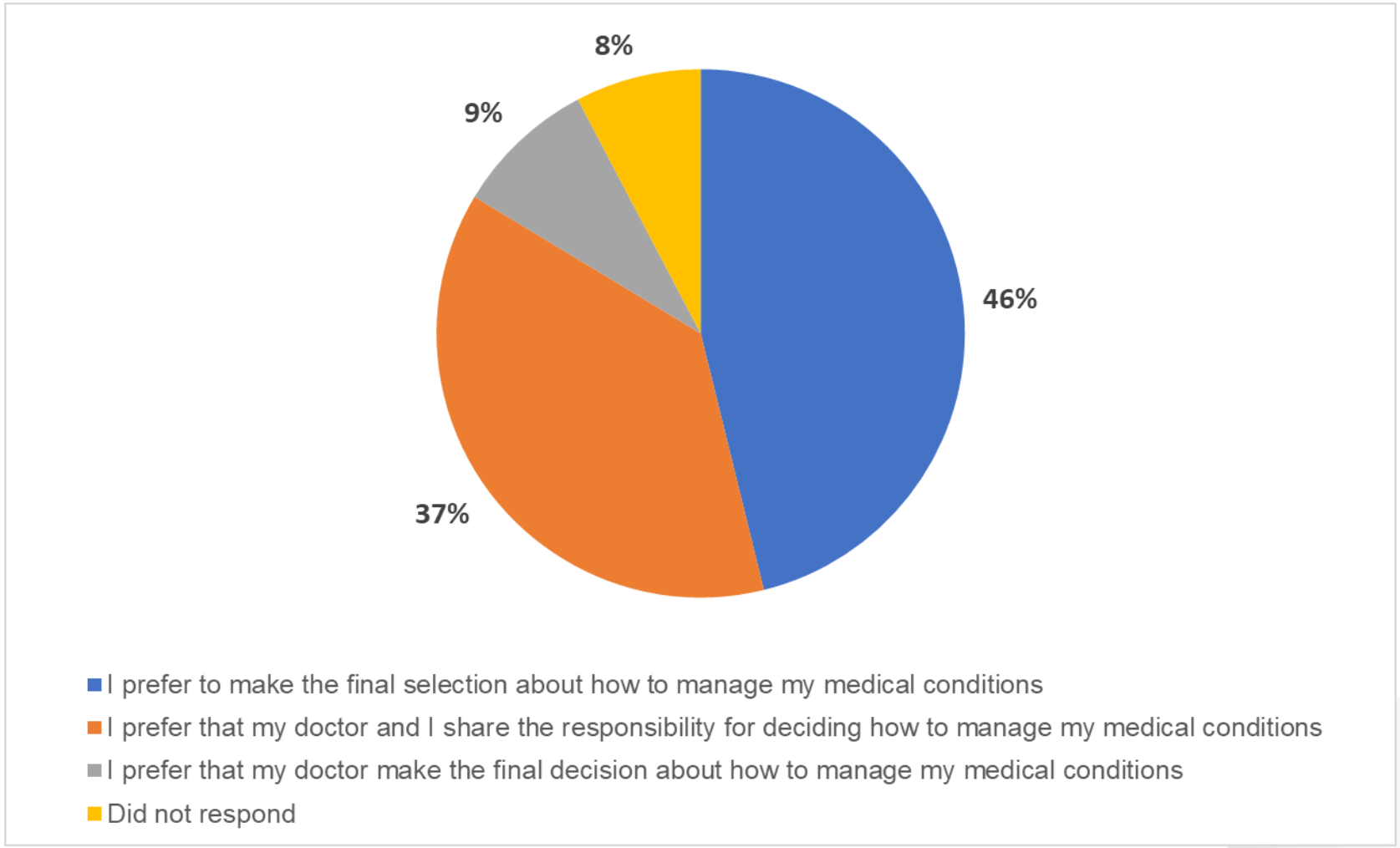
After they have all the information they need about their illness and possible medications and behavioral treatments, some patients prefer to leave decisions about managing their medical conditions up to their doctor, while others prefer to participate in…..



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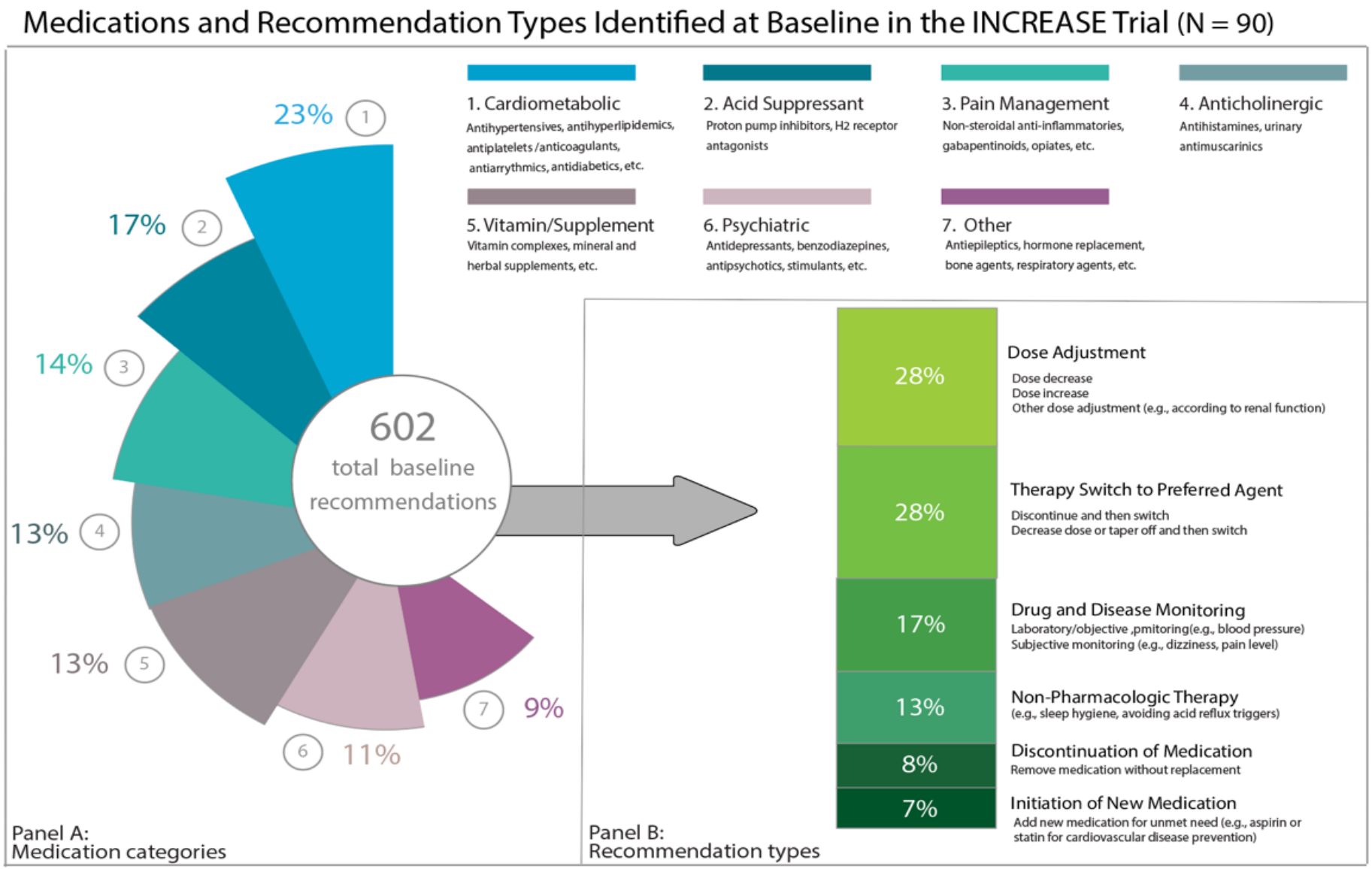
A Closer Look at Medication Problems



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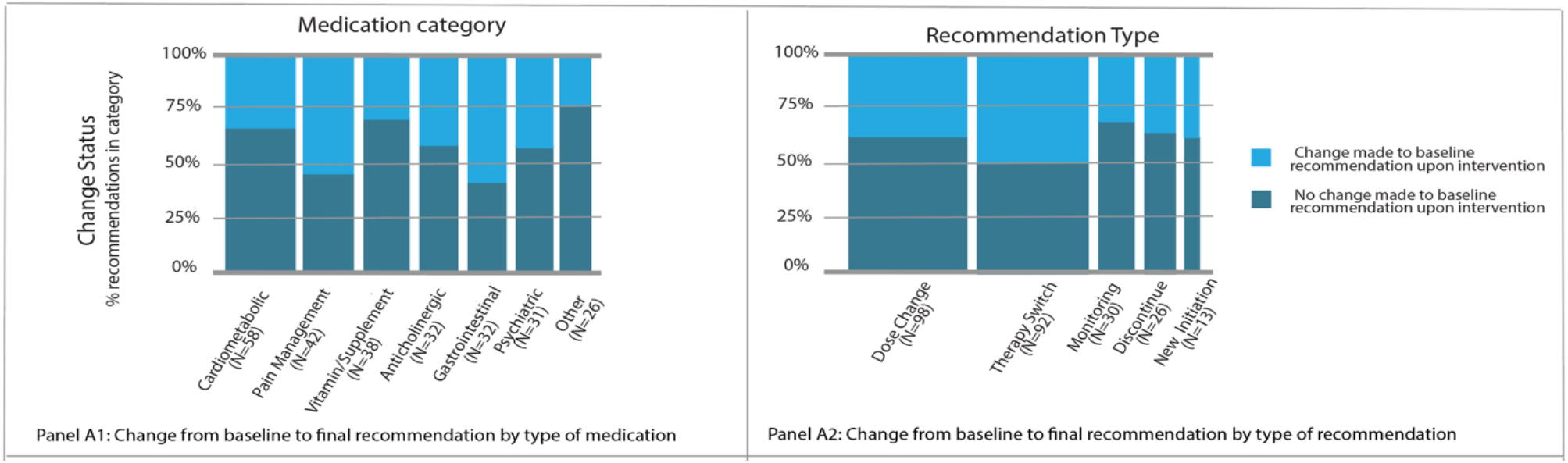
Change Is Never Easy



Panel A1: Change from baseline to final recommendation by type of medication

Panel A2: Change from baseline to final recommendation by type of recommendation

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Measuring Cognitive Reserve

Expectation: Participants will perform worse or the same under challenged conditions compared to non-challenged conditions

Reality: Some participants performed better under challenged conditions

TMTB challenged (sec)	TMTB unchallenged (sec)	Notes
44	40	
107	82	
300	112	
73	40	
94	192	4 errors unchallenged testing
230	87	
69	52	
61	67	
133	185	1 error challenged vs 2 errors unchallenged testing

Fall Prevention

- ✓ **Fall risk screening**:
  - ➢ Vital signs (all visits)
  - ➢ Clinician assessment of risk (enrollment)
  - ➢ Gait and balance testing (all visits)
    - ❖ 3-Stage Balance Test (wearing Opals)
    - ❖ Walk (on GAITRite, wearing Opals)
    - ❖ 5x Sit to Stand
- ✓ **Study partner** (study eligibility)
- ✓ **Referral** to PT for those at higher risk based on gait and balance testing
- ✓ **Educational materials** to decrease risk of falls – all participants

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Fall Prevention (cont.)

Color code	Follow up steps	Materials
Green: no/low risk	None needed – could provide information on fall risks/prevention if this is not already offered (how to prepare your home, etc.)	STEADI Older Adult Fact Sheet Check for Safety Brochure Stay Independent Checklist
Yellow: more than one risk factor	Education on risk factors, referral to community-based exercise programs, provide information on fall risks/prevention	STEADI Older Adult Fact Sheet Check for Safety Brochure Stay Independent Checklist ** identification of challenges from testing: e.g., gait speed** Community Based Programs in the Bluegrass Area
Orange: *extended* time to complete 5 X STS and Gait speed for age/gender	Recommend follow up with physical therapy for examination of more specific challenges, referral to community-based exercise programs, provide information on fall risks/prevention	STEADI Older Adult Fact Sheet Check for Safety Brochure Stay Independent Checklist ** identification of challenges from testing: e.g., gait speed** Community Based Programs in the Bluegrass Area
Red: unable to complete key components of examination	Recommend follow up with physical therapy for examination of more specific challenges, referral to community-based exercise programs, provide information on fall risks/prevention	STEADI Older Adult Fact Sheet Check for Safety Brochure Stay Independent Checklist ** identification of challenges from testing: e.g., gait speed** Community Based Programs in the Bluegrass Area

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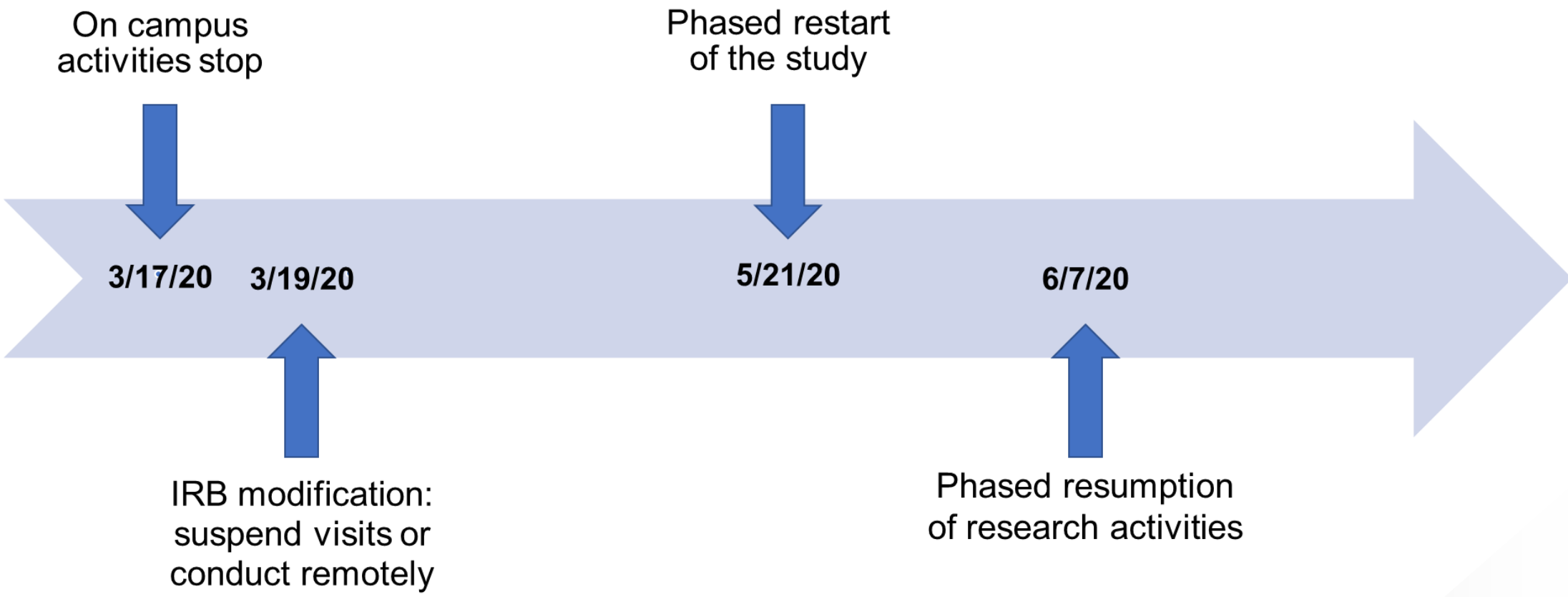
COVID-19: Protocol Changes



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COVID-19: Impact on Data Collection

- Medication optimization interventions and active data collection on adverse events switched from in-person to remote
- Follow-up extended until in-person visits could resume for evaluations where remote modalities were not feasible (e.g., cognitive testing),
- Hybrid visits (short in person + remote) implemented when in-person visits could resume
- COVID-19 testing for all staff and participants before entering the clinic

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Some Final Thoughts

- Deprescribing interventions are not the typical interventions
- Most patients want to be actively involved in managing their chronic conditions
- Things don’t always work as planned, so prepare for the unexpected
- Investigators don’t always have full control
- Participant safety is the most important aspect of conducting a study

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Thank you!