Spinal Manipulation and Dry Needling vs. Botox Injections in the Management of Chronic Migraine: A Randomized Non-Inferiority Controlled Trial Protocol

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Migraine

2: Rank in the world's causes of disability

- Global Burden is Disease study in 2019 (Steiner et al., 2020)
  - Following low back pain
  - #1 in young women (15-49 years)

Types

- Episodic (<15 headache days/month)
- Chronic (≥ 15 headache days/month)
  - Less common but most disabling (more headache days) (Katsarava et al., 2012)

High prevalence of neck pain (Al-Khazali et al., 2022)

- Cervical musculoskeletal disorders (Liang et al., 2019)

Treatment Options

Oral Medications (American Headache Society)

- Poor efficacy and tolerability
- Low treatment persistence
- Potential for overuse (Hepp et al., 2015, 2017)

Targeted Conservative Alternatives

- Local injections
  - Botulinum toxin A (Botox®)
- Physical Therapy
  - Spinal manipulation
  - Dry needling
  - ** High prevalence of neck pain in migraine*

Botox®

1st and only FDA-approved preventive specific for chronic migraine

- Superior to placebo
  - Meta-analysis of 10 years of real-world data (Lanteri-Minet et al., 2022)
- Approved protocol since 2010 (Blumenfeld et al., 2010)
  - 2 rounds; 3 months apart
- Selected facial and neck muscles

Disadvantages

- Adverse events
  - eyelid ptosis and muscle weakness
  - Rare complications: dysphagia, botulism, and sometimes death (systematic spread of the toxin)
- Cost
  - $3,000 (unaffordable, decreased compliance)

Physical Therapy: Spinal Manipulation (SM)

Effective for headaches

- Cervicogenic type (Bini et al., 2022; Fernandez et al., 2020)
  - Presence of neck pain from cervical joint impairments

Types

- Thrust or Non-thrust
  - Upper cervical, cervicothoracic

Relatively safe (Peters et al., 2022; Swait & Finch, 2017)

- Benign adverse events
  - symptom aggravation, stiffness, lightheadedness
- Extremely rare complications
  - cervical artery dissection and disc herniation exacerbation

Physical Therapy: Dry Needling (DN)

Effective for headaches

- Cervicogenic type (Pourahmadi et al., 2021; Vázquez-Justes et al., 2022)
  - Presence of neck pain from muscular trigger points

Solid filiform needle

- FDA Class II medical device
- Selected facial and neck muscles

Relatively safe (Boyce et al., 2020; Gattie et al., 2020)

- Benign adverse events
  - pain during and after treatment, bleeding, and bruising
- Extremely rare complications
  - prolonged symptom aggravation, fainting, and forgotten needles during dry needling

Aim

Compare the effectiveness of SM and DN as non-inferior to Botox® in patients with chronic migraine

Hypothesis

- SM and DN are at least as good (not unacceptably worse) as Botox®
- However, SM would be more effective than DN

Theory

- Universal mechanism: Inhibition of inflammatory mediators affecting the trigeminocervical complex (Aoki AR, 2005; Bialosky et al., 2018; Dommerholt J, 2011)
- Botox® is the assumed treatment standard
  - FDA approval and abundance of evidence
- SM and DN (though not superior) may be potential alternatives
  - Cost-effectiveness and relative safety
- SM has more evidence; DN is relatively new

Ethics

- No placebo

Research Design

Multi-center, multi-arm, parallel, randomized, non-inferiority controlled trial

Population

- Adult patients diagnosed with chronic migraine (International Classification of Headache Disorders, 2018)
- Veterans Affairs (VA) healthcare system in the Southeast region

Intervention

- Active Control (C): Botox®
  - FDA approved protocol (Blumenfeld et al., 2010)
  - 2 rounds; 3 months apart
- Test Treatment 1 (T1): SM
  - Thrust and non-thrust to the upper cervical and cervicothoracic regions (impairment-based) (Dunning et al., 2016)
  - Frequency: 1/week x 4 weeks (4 sessions); 2 rounds; 2 months apart
- Test Treatment 2: DN
  - Facial and neck muscles (impairment-based) (Mousavi-Khatir et al., 2021)
  - Frequency: 1/week x 4 weeks (4 sessions); 2 rounds; 2 months apart

Research Design

Multi-center, multi-arm, parallel, randomized, non-inferiority controlled trial

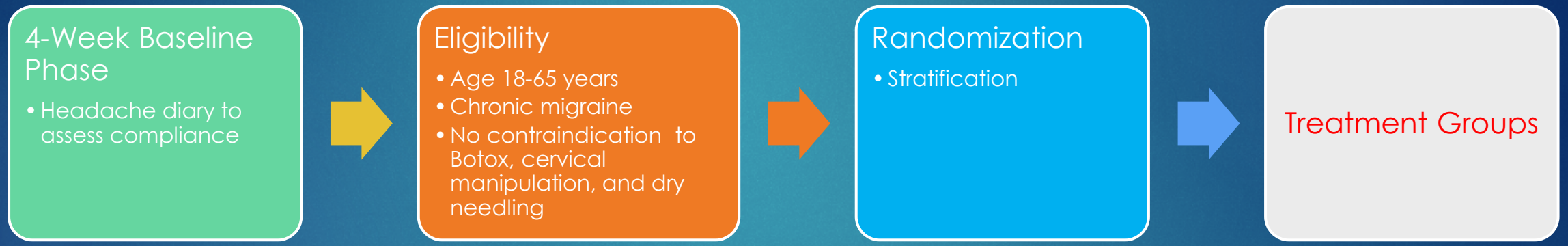
Endpoints (change from baseline) (International Headache Society Guidelines, Tassorelli et al., 2018)

- Primary
  - # Headache days/month
- Secondary
  - Intensity, medication usage, Beck Depression Inventory, Global Rating of Change, Migraine Functional Impact Questionnaire, Headache Disability Index, Migraine Disability Assessment, Headache Impact Test-6, Neck Disability Index

Research Design

Multi-center, multi-arm, parallel, randomized, non-inferiority controlled trial

Study Protocol Flow Diagram



Research Design

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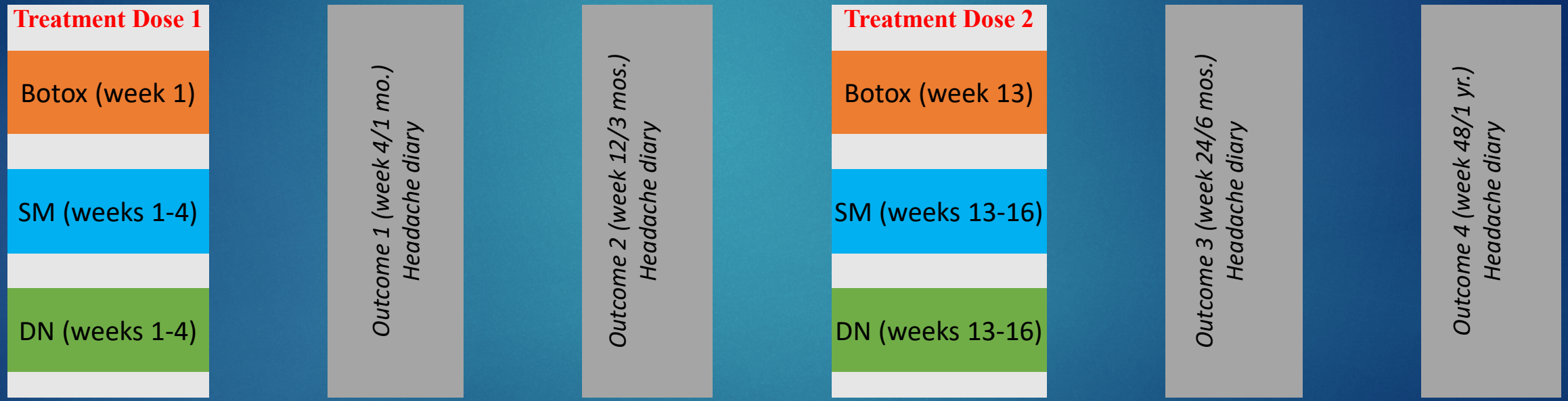
Treatment Flow Diagram



Research Design | Statistical Analyses

Power Analysis

- Total sample size = 78 (26/group) (Cleveland Clinic Sample Size Calculator, Wang and Ji, 2020)
  - Non-inferiority margin (M) (US FDA Non-Inferiority Guidance., 2016)
    - Primary endpoint - systematic review with meta-analysis (Lanteri-Minet et al., 2022)
      - Mean difference of random effects model
      - -10.4 (-11.35, -9.46) headaches days change from baseline
    - M_1 = lower bound of the 95% confidence interval (CI)
    - M_2 = 50% discount of M_1 **combined** with the largest clinically acceptable difference (degree of inferiority) of T compared to C (effect size of 0.8)
  - Power = 0.8
  - Type 1 error rate = 0.5
  - Attrition rate = 20%

Statistical Analyses

Data Analysis

- Inferential Statistics
  - Mixed-model analysis of variance (each outcome)
  - Multiple comparison procedures
    - Between subjects factors (treatment groups)
    - Within subjects factors (time)
  - Effect sizes
- Clinical Statistics
  - Intention-to-treat analysis
  - Per-protocol analysis
  - Number needed to treat

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IRB approval

- VA health system

Trial registration

- Clinicaltrials.gov

Level of pragmatism

- Pragmatic-Explanatory Continuum Indicator Summary (PRECIS-2) (Loudon et al., 2015)

Reporting

- Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement (Piaggio et al., 2012)