2nd Annual GI ReConnect

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SANTA FE, NEW MEXICO

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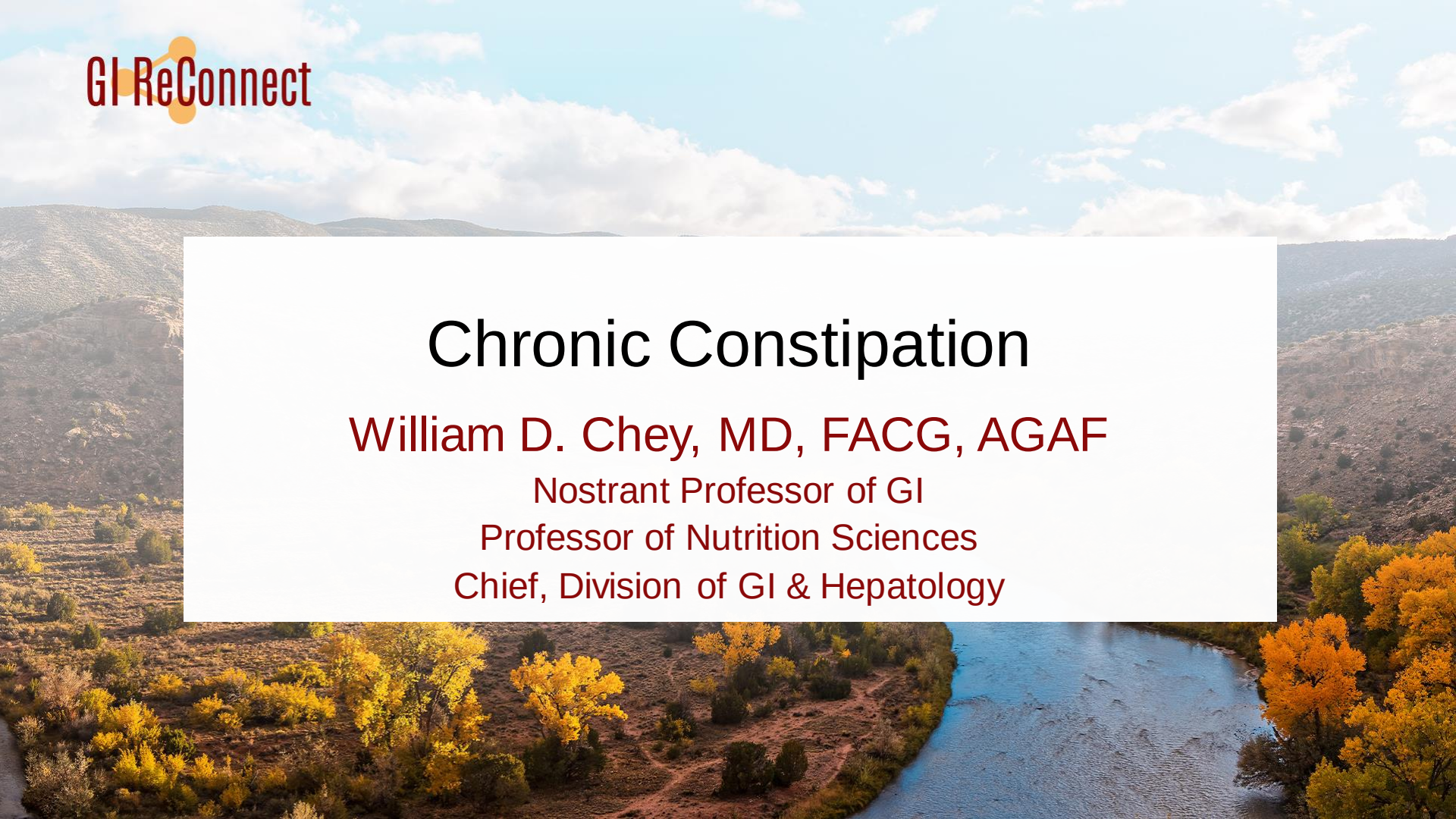

GI ReConnect

Chronic Constipation

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Disclosure Statement

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All additional planning committee members, the University of Cincinnati staff and the Gi Health Foundation staff have no relationships to disclose.

Faculty Disclosures

- Consultant: Allakos, Abbvie, Alnylam, Arelyx, Arena, Bayer, Biomerica, Ironwood, Nestle QOL Medical, Salix/Valeant, Takdeda, Urovant, Vibrant
- Stock Options: GI on Demand, Isothrive, Modify Health
- Research Grant: Commonwealth, QOL Medical

An Office-Based, Point-of-Care Rectal Expulsion Device (RED) Predicts Treatment Outcomes With Pelvic Floor Physical Therapy Among Patients With Chronic Constipation

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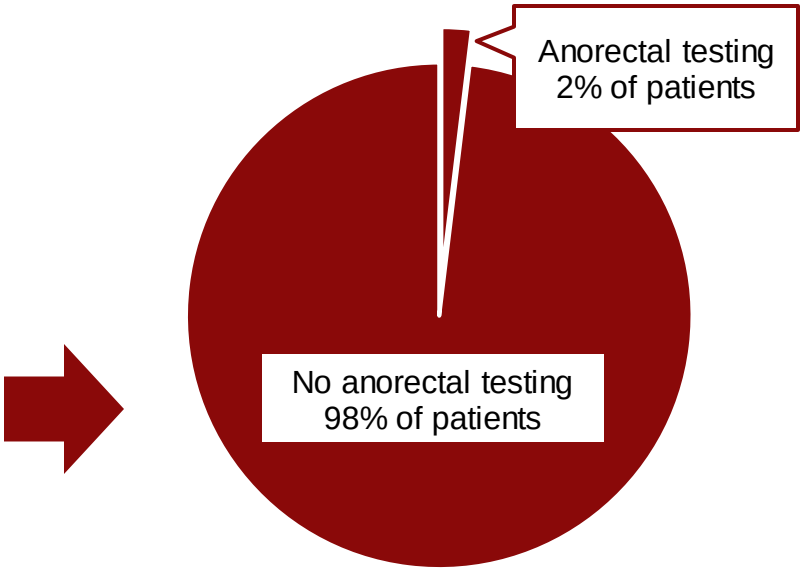
Anorectal Function Testing Is Broadly Underutilized



US Survey of Individuals with Chronic Constipation
(n=1,768 care-seeking patients)

- 2-8 million patients referred to gastroenterologists each year for constipation
- Laxative refractory CIC patients are enriched for an evacuation disorder
- Few undergo anorectal function tests

Oh S et al. *Am J Gastroenterol*. 2020;115(6):895-905; Singh et al. *Clin Gastroenterol Hepatol*. 2007 Sep;5(9):1053-8; *Am J Gastroenterol.* 2015; 110:572–579*; Am J Gastroenterol.* 2014; 109:250–256.

RED (Rectal Expulsion Device)

- Provides a simple screening test for evacuation disorders
- Enables point-of-care testing
- Provide actionable, binar test results in the office o the lab

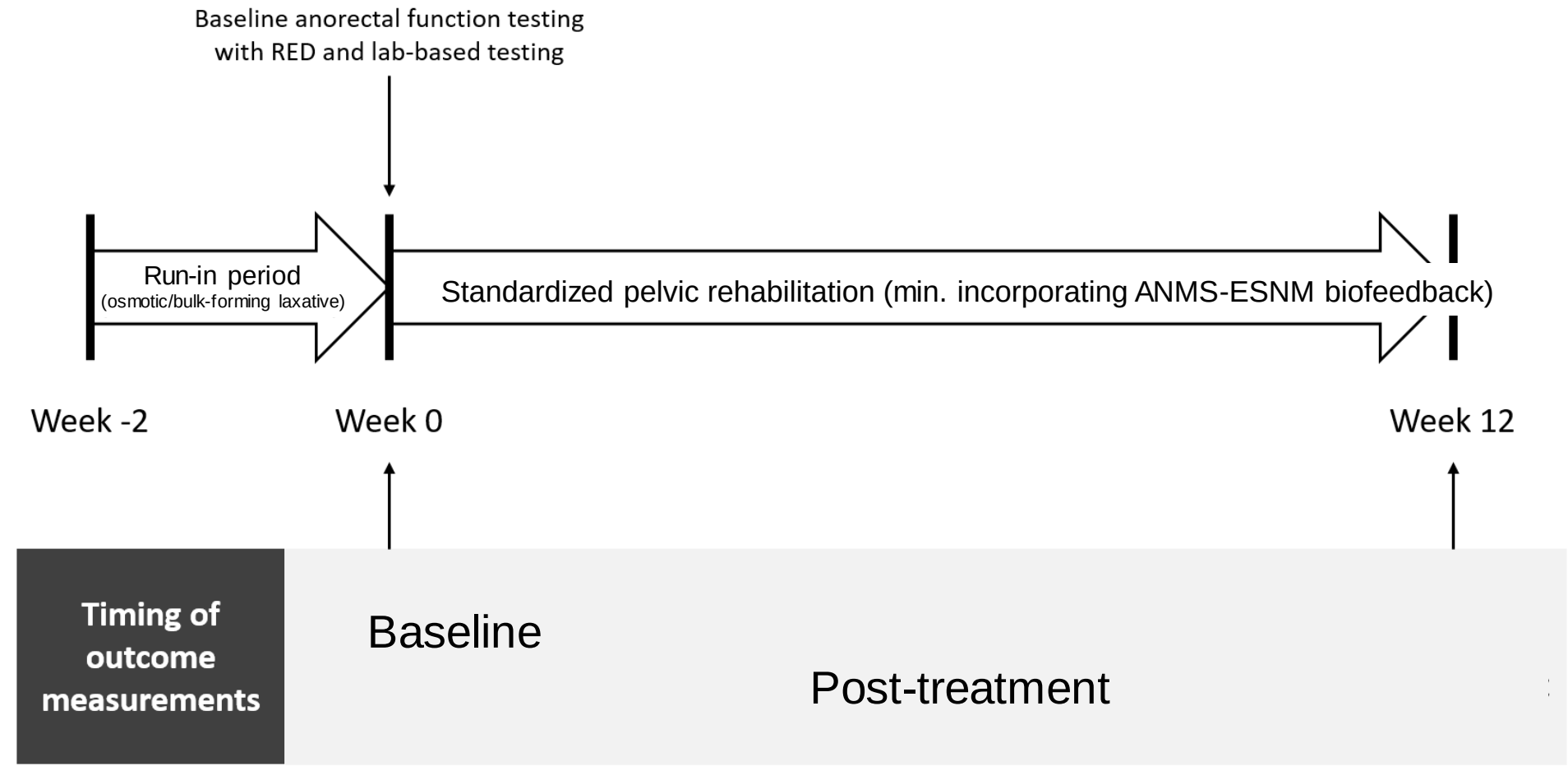
Shah E et al. *Am J Gastroenterol*. 2018;113(11):1613-1620;
Chey W, Baker JR, Watts L, Harris A, Shah ED. *CGH*. Published Dec 1, 2021. doi: 10.1016/j.cgh.2021.11.034.

Aim

To evaluate the **predictive accuracy** of RED on clinical outcomes with community-based pelvic floor physical therapy

In other words:

Can RED inform clinical outcomes in practice?


Baseline anorectal function testing
with RED and lab-based testing
Run-in period
(osmotic/bulk-forming laxative)
Standardized pelvic rehabilitation (min. incorporating ANMS-ESNM biofeedback)
Week -2
Week 0
Week 12
Timing of outcome measurements
Baseline
Post-treatment

Protocol for Use of RED

1. Device inserted into rectum after DRE in left lateral position

2. Device inflated by removing cap on device

3. Expulsion attempted in privacy: 2 minutes in a left lateral position. If not expelled, then 2 minutes in a seated position

Outcomes Defined by Clinical Response to Community-Based Pelvic Floor Physical Therapy

- Primary outcome: Global clinical response
  - Achieving a minimal clinically important difference (MCID) in PAC-SYM score reduction ≥0.75 at 12-weeks *vs*. baseline
- Secondary outcome: Disease-specific HRQoL
  - Achieving a MCID in PAC-QOL score reduction ≥10 at 12-weeks *vs*. baseline
- Secondary outcome: Weekly CSBM responder
  - Achieving at least 3 weekly CSBMs at week 12 with increase of 1 CSBM/week compared to baseline

Study Participants

- 60 adult patients meeting Rome IV FC criteria enrolled between January to June 2021 (safety population)
- 52 patients included in intention-to-treat analysis completing at least 1 physical therapy appointment
  - Median of 3.0 PT appointments attended (range 1-7)
  - At baseline: 21.7% of patients had at least 3 CSBM/week
- One adverse event: anal pain (n=1) due to suspected fissure
- No serious adverse events

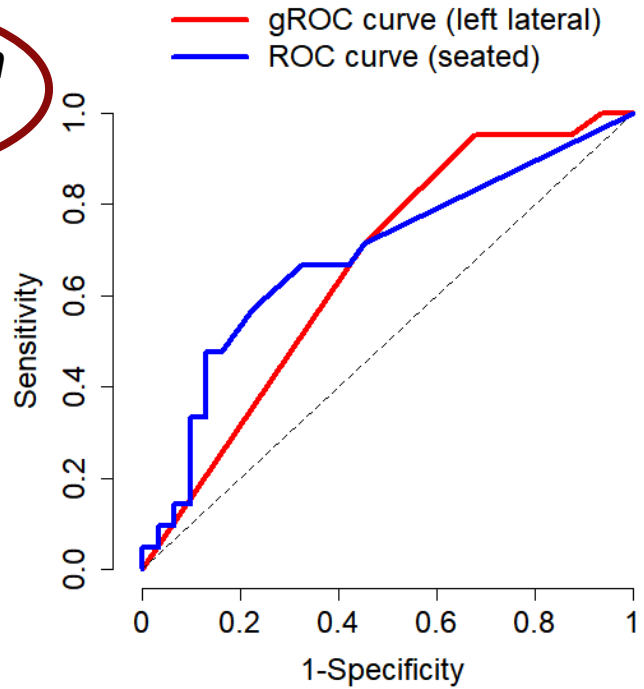
Results

Global sym response

HRQoL respons

Bowel symptom response

Testing method	PAC-SYM	PAC-QOL	CSBM 3+1 responder
Left lateral	0.67 p<0.001	0.67 p<0.001	0.63 p<0.001
Seated*	0.69 p=0.009	0.65 p=0.058	0.63 p=0.095

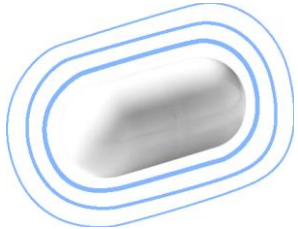


*Patients are given a 2-minute trial in left lateral before trying seated.

Conclusions

- RED is an investigational point-of-care device designed for use during the initial office consultation for chronic constipation.
- RED appears capable of identifying patients with a low likelihood of response to community-based pelvic floor physical therapy in the left lateral position.
- RED appears capable of informing the likelihood of response to pelvic floor physical therapy delivered in the community.

Efficacy & Safety of Vibrant capsule for Chronic Idiopathic Constipation (CIC): Randomized, Double-Blind, Multicenter, Placebo-controlled, Phase III Trial



Satish SC Rao, EMM Quigley, WD Chey, Sharma A, K Freidenberg, AJ Lembo, et al, and Vibrant Study 270 Investigators, USA

AUGUSTA UNIVERSITY

Background

- 45% of constipated patients remain dissatisfied with current drug therapies, suggesting a need for new therapies
- There is growing interest in mechanical stimulation of the colon
- In preliminary studies, a Vibrating Capsule (Vibrant Ltd, Yokenam, Israel) improved constipation symptoms, possibly by augmenting circadian rhythm

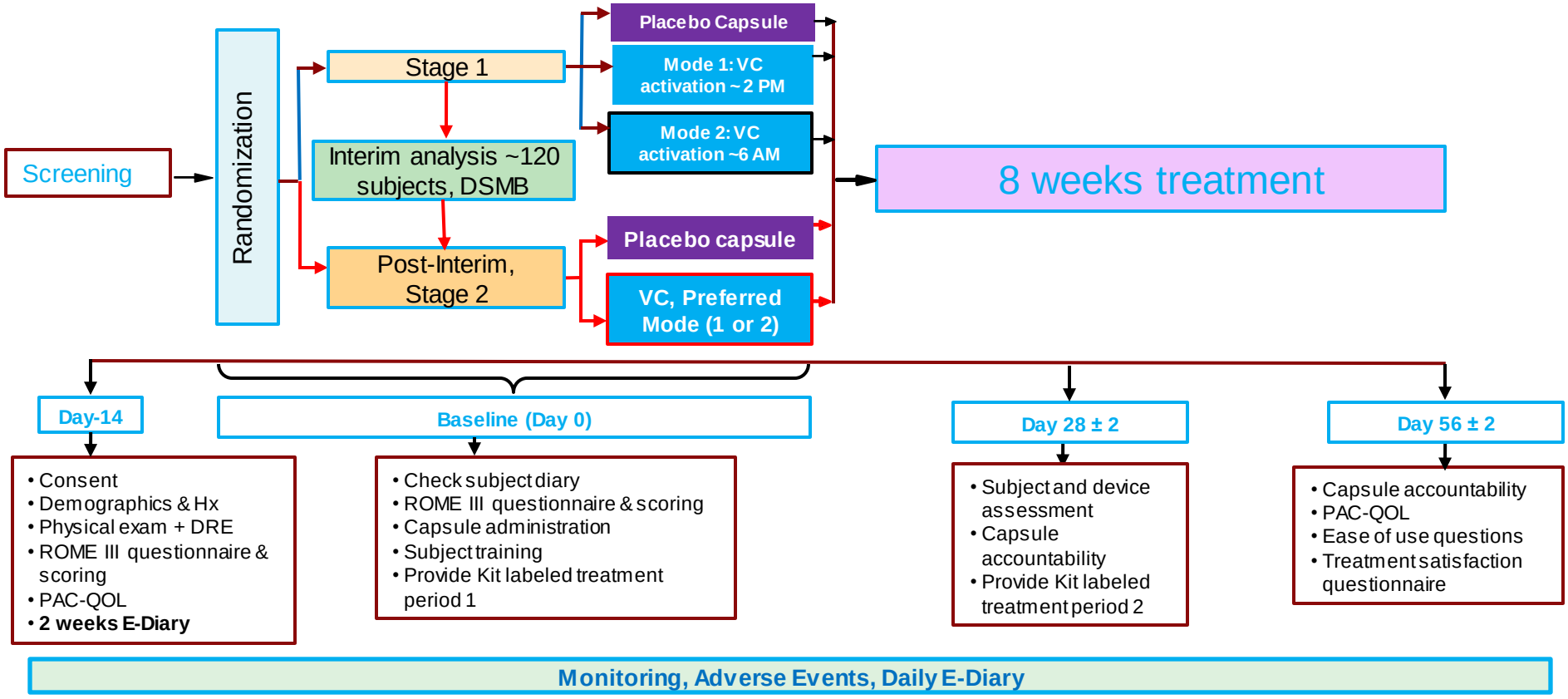
Ron Y et al. *NGM.* 2015; Rao SSC et al. *NGM.* 2020.

Hypothesis

Aim

- Conduct a prospective, randomized, double-blind, placebo-controlled, multi-center, 3-arm study, (2 active arms + 1 placebo), to examine the efficacy and safety of the vibrating capsule in patients with chronic constipation

Vibrating Capsule (VC), Phase III Study Protocol



Vibrating Capsule System

Vibration Capsule Program
Two Stimulation Cycles, each ~ 2 hours:
Each Vibration cycle: 3 seconds on and 16s rest

Vibrating capsule

Activation POD:

- **Used for activating the capsule**

E-Diary: Patient Reporting APP

- Daily stool data
- Symptoms
- Capsule ingestion information
- Compliance
- Rescue
- Adverse Events

Primary and Secondary Outcomes & Analysis

Primary Endpoints

- CSBM1 success rate – an increase of at least 1 CSBM/week relative to run-in, and during at least 6 of the 8 weeks of treatment

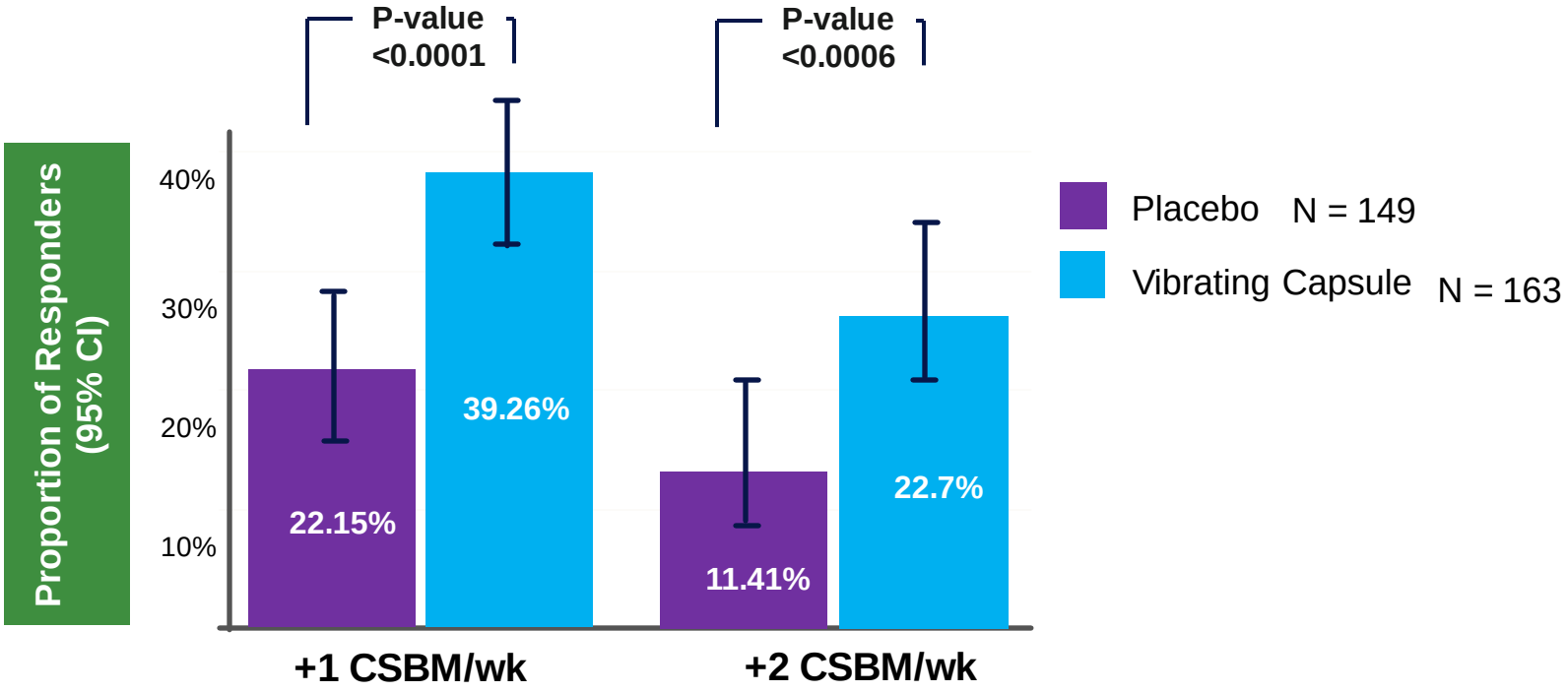
OR

- CSBM2 success rate – an increase of at least 2 CSBM/week relative to run-in, and during at least 6 of the 8 weeks of treatment
  - SBM: A spontaneous BM without use of laxative/enema/suppository for previous 48 hours
  - CSBM: A complete SBM

Secondary Endpoints

- Change from baseline in:
  - Straining effort
  - Stool consistency (Bristol Stool Scale)
  - Bloating
- Quality of Life (QoL)
  - Total Score
  - Individual domains (Physical, Psychosocial, Worries, Satisfaction)
- Safety during 8 weeks of treatment
- *Data were analyzed using Intention to Treat (ITT) analyses*

Effect of Vibrating Capsule on CSBM, Primary Outcomes

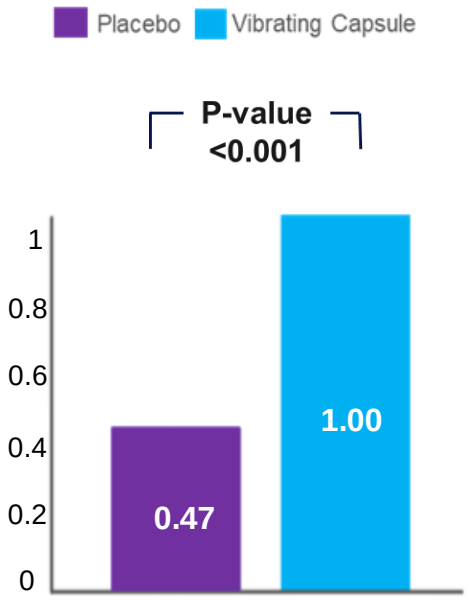


Incremental CSBM (Complete spontaneous bowel movement)

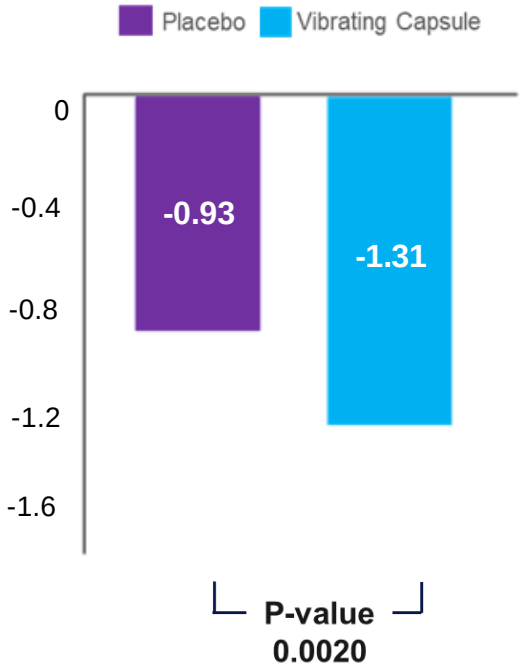
Effects of Vibrating Capsule on Straining, Stool consistency and QOL

Straining score

Stool consistency



QOL



Adverse Events

Adverse event	Vibrating Capsule, Mode 1 (n=163) No. of patients (%)	Vibrating Capsule, Mode 2 (n=37) No. of patients (%)	Placebo (n=149) No. of patients (%)
Adverse events during treatment (combined safety populations including interim analysis groups).*			
Any event	44 (27.0)	9 (24.3)	26 (17.4)
Vibrating sensation/discomfort	18 (11.0)	1 (2.7)	.
Headache	3 (1.8)	1 (2.7)	4 (2.7)
Urinary tract infection	3 (1.8)	1 (2.7)	2 (1.3)
Abdominal pain/discomfort	4 (2.5)	.	8 (5.4) 1 SAE
Vomiting	2 (1.2)	2 (5.4)	1 (0.7)
Nausea	3 (1.8)	.	1 (0.7)
Abdominal distention	1 (0.6)	.	2 (1.3)
Anorectal problem	1 (0.6)	.	5 (3.4)
Diarrhea	2 (1.2)	.	.
Covid-19	1 (0.6)	.	2 (1.3)
Nasopharyngitis/Bronchitis	4 (2.5)	1 (2.7)	4 (2.7)
TIA	.	.	1 (0.7) SAE
Musculoskeletal	2 (1.2)	.	1 (0.7)
*Data shown for adverse events in at least 1% of the subjects			

Summary

- The Vibrating Capsule significantly increased the number of CSBM1 ($p<0.0001$) and CSBM2 ($p=0.0011$) compared to placebo in patients with chronic constipation, and met both primary outcome measures
- The straining effort to defecate ($pp=0.0126$) and stool consistency ($p<0.0001$) significantly improved with VC compared to placebo, but not bloating
- The overall Qol ($p=0.0020$) and all Qol domains significantly improved with VC
- The onset of increase in CSBMs occurred within 1-2 weeks and was sustained
- The adverse event profile of VC was comparable to placebo

Constipation Nuggets

- Online survey of 24,089 US adults
  - 5.7% (n=1,367) met R4 criteria and/or reported a physician diagnosis.
  - Of these, 20.7% were undiagnosed, 38.2% had PD only and 41.1% met both R4 and had a PD (Lacy et al. Mo1084)
- Same survey, 2,105 met Rome IV criteria for CIC.
  - 28.9% (n=608) CIC patients reported currently taking an Rx medication
  - CIC patients taking an Rx reported higher overall satisfaction with control of bowel symptoms (49.3%, [n=300] vs. 27.2% [258]; $p<0.001$), and abdominal symptoms (48.8% [n=297] vs. 29.8% [283], $p<0.001$) than patients taking an OTC
  - Linaclotide most common prescription med (29%) (Lacy et al Tu1339)

Constipation Nuggets

- Concordance between history and a stool diary for key constipation symptoms such as stool frequency, stool consistency, use of digital maneuvers, frequency of incomplete BMs and straining effort, was poor (30-50%) in a clinic setting. To accurately characterize symptoms, a prospective stool diary is recommended (Hudgi et al. Tu1330)
- Constipation Diary©APP accurately recorded bowel-related symptoms in constipated patients. The APP provides a detailed daily stool log and electronic summary report providing useful information to physicians and researchers (Yan Tu1344)