PATIENT-CENTERED OUTCOME PROJECT UPDATE

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University of New Mexico

DISCLOSURES

- Research support from the National Institutes of Health (P20 GM109899; U54 NS116025, R03AG075408, R01DC18282, P20GM109089) Department of Defense (W81XWH-19-CTRR-CTA)

- Clinical Trial support (Pharma 2B, AEON, ADDEX, SCION, JAZZ, MJFF)

DYSTONIA COALITION

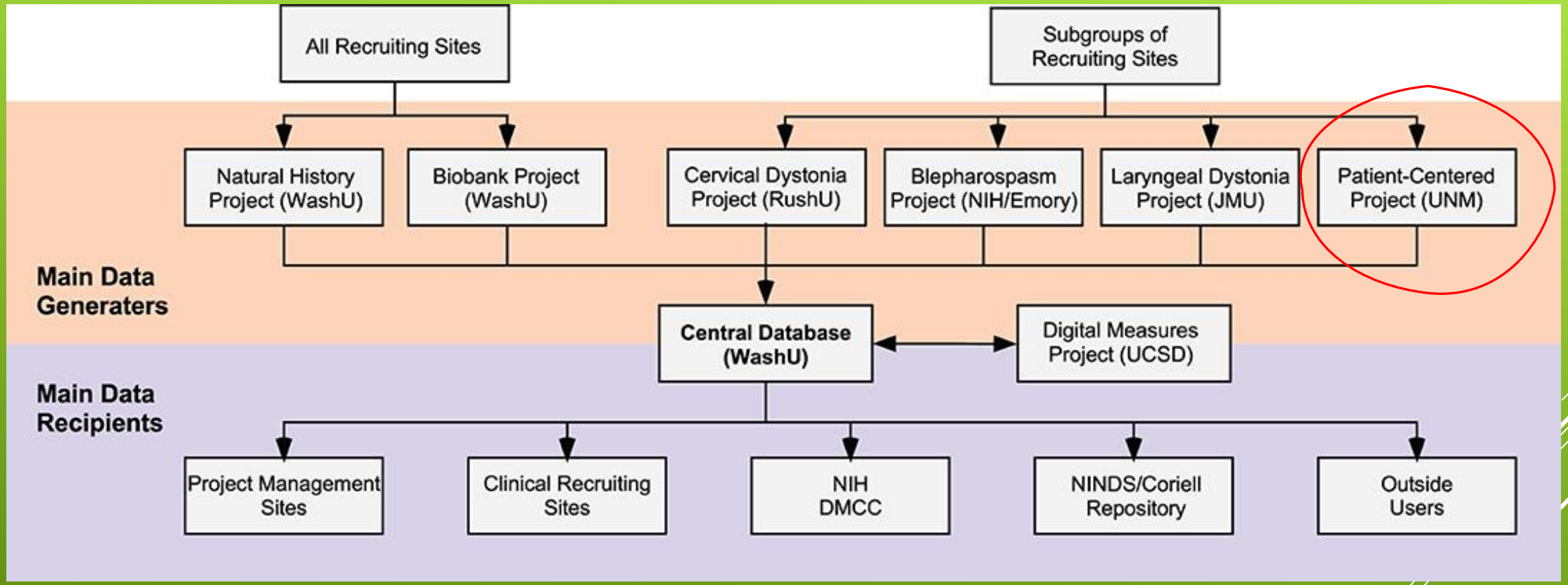
AGENDA

- BACKGROUND
- PCO DEVELOPMENT
  - SPECIALIST PANELS
  - SURVEY
- APP DEVELOPMENT
- PCO VALIDATION
  - TRAINING
  - YR 5 RECRUITMENT
- FUTURE DIRECTIONS

DYSTONIA COALITION

BACKGROUND

DYSTONIA COALITION



Kilic-Berkmen et al. Front. Neurol., 08 April 2021 | https://doi.org/10.3389/fneur.2021.660909

DYSTONIA COALITION

MAIN GOAL

To provide *key data* to establish clinical trial readiness in future clinical trials for novel treatments for dystonia.

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> BoNT is 1st line therapy

> Lifelong condition requiring use of this therapy for decades possibly

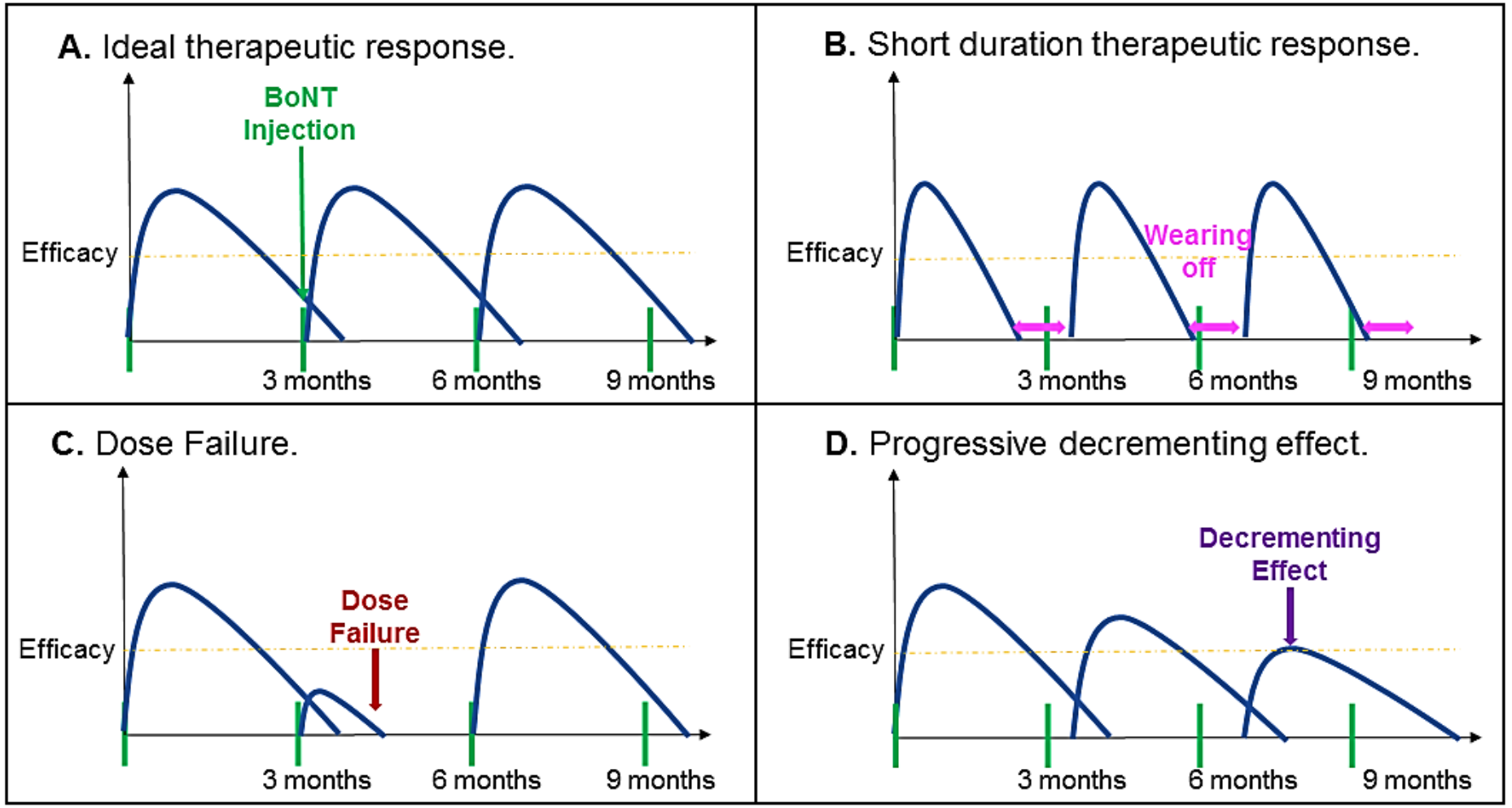
> BoNT produces significant motor improvements, QOL and pain

> Yet, 1/3 of patients discontinue use of BoNT

> Disability may not improve to meet patient expectations despite improvement seen by standard clinical rating scales

DYSTONIA COALITION

Figure 2. Fluctuations in severity over time and complications of therapy.



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Develop a Patient-Centered Outcome (PCO) measure

- Cervical dystonia
- Blepharospasm
- Laryngeal dystonia

Implement PCO in app-based format

- sensitive to change
- feasible for use on frequent/weekly time scale

Characterize therapeutic response to BoNT over time

- measure effect size
- capture yo-yo effect
- prepare for future adjunct clinical trial

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PCO DEVELOPMENT

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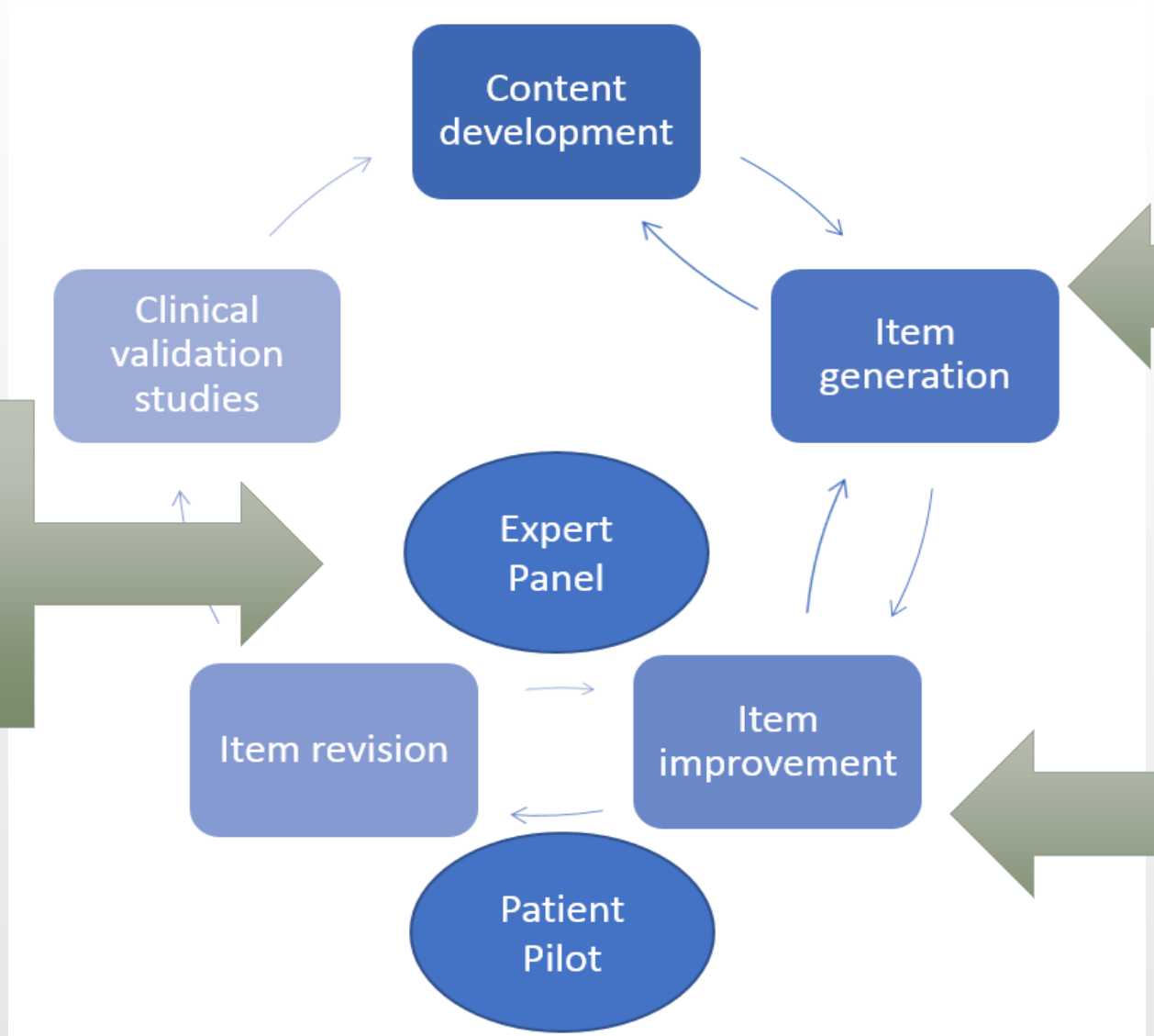


DC data previously collected from 600 enrollees on outcome measures

CD/BSP/LD Expert Panels assembled (experts, patients & PAG representatives)

Patient focus groups for item generation and item improvement

DYSTONIA COALITION

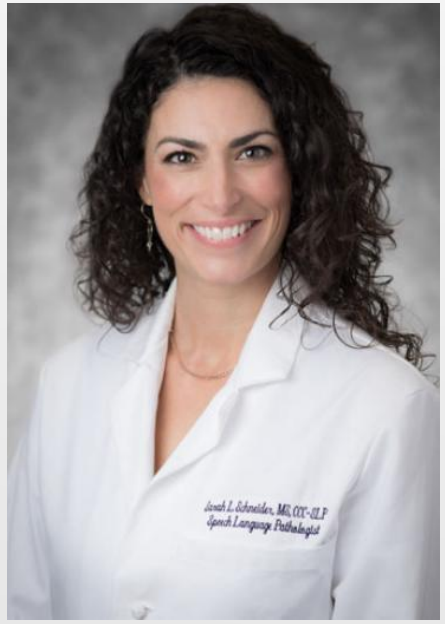
PCO OVERALL CHARACTERISTICS

- 3 domains
  - Motor symptoms
  - Activities (disability)
  - Psychosocial (including QOL)
- 14-16 questions
- Attempted to overlap items and wording consistency across PCOs
- Guidance from FDA through process

DYSTONIA COALITION

BSP PANEL CHAIR:
Brian D. Berman MD, MS
Division Chair
Director of PMDC
Professor
Virginia Commonwealth University

LD Panel Chair:
Sarah L. Schneider MS, CCC-SLP,
Co-Director
UCSF Voice and Swallowing Center
University of California San Francisco

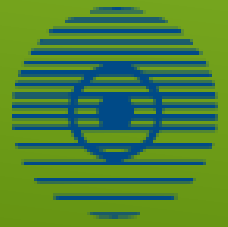


Statistician:
Fares Qeadan PhD, MS, MES
Associate Professor
Biostatistics
Loyola University Parkinson School of Health Sciences &Public Health

DYSTONIA COALITION

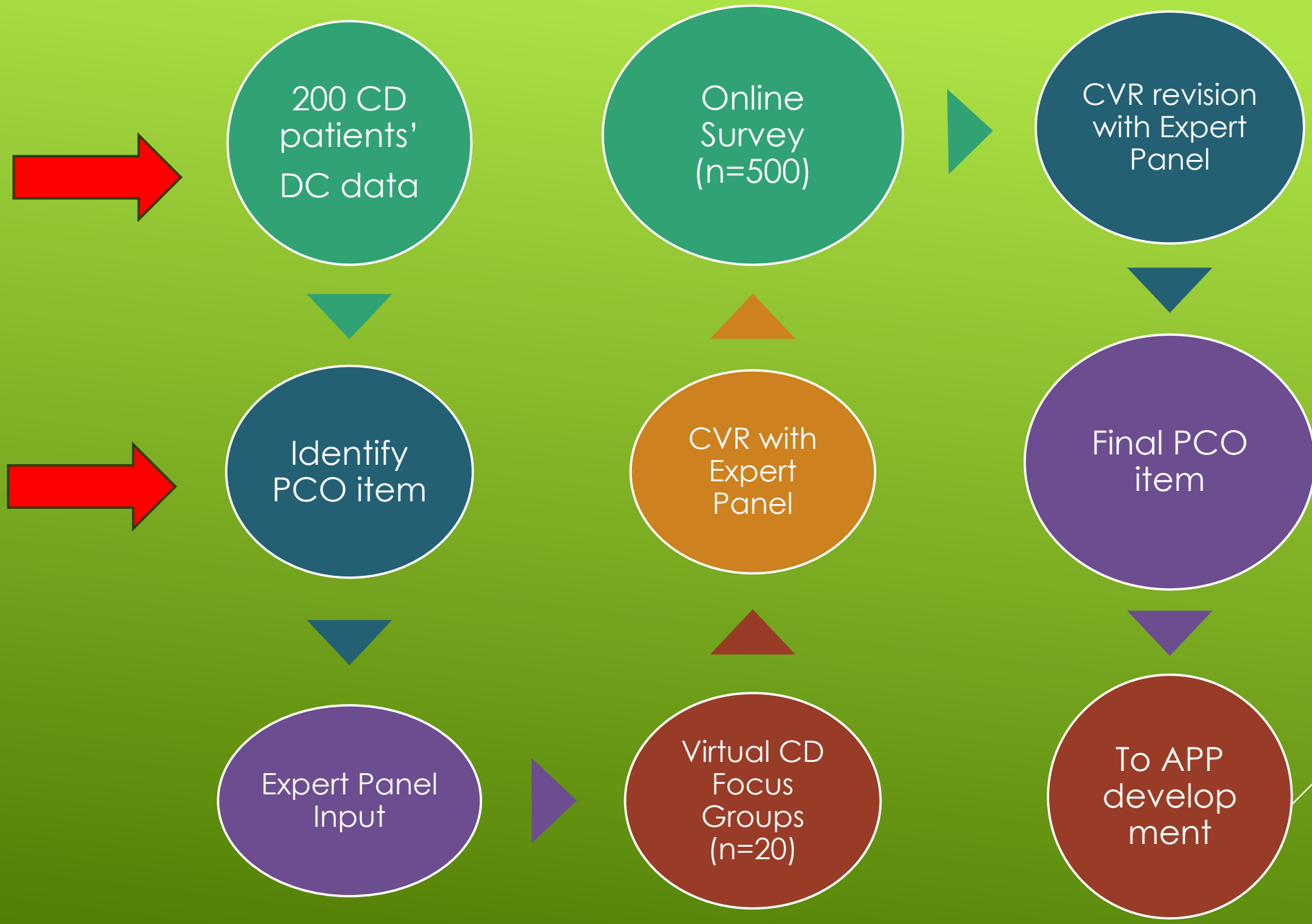
DYSTONIA
MEDICAL RESEARCH FOUNDATION

DYSPHONIA
INTERNATIONAL
FORMERLY NATIONAL SPASMODIC DYSPHONIA ASSOCIATION



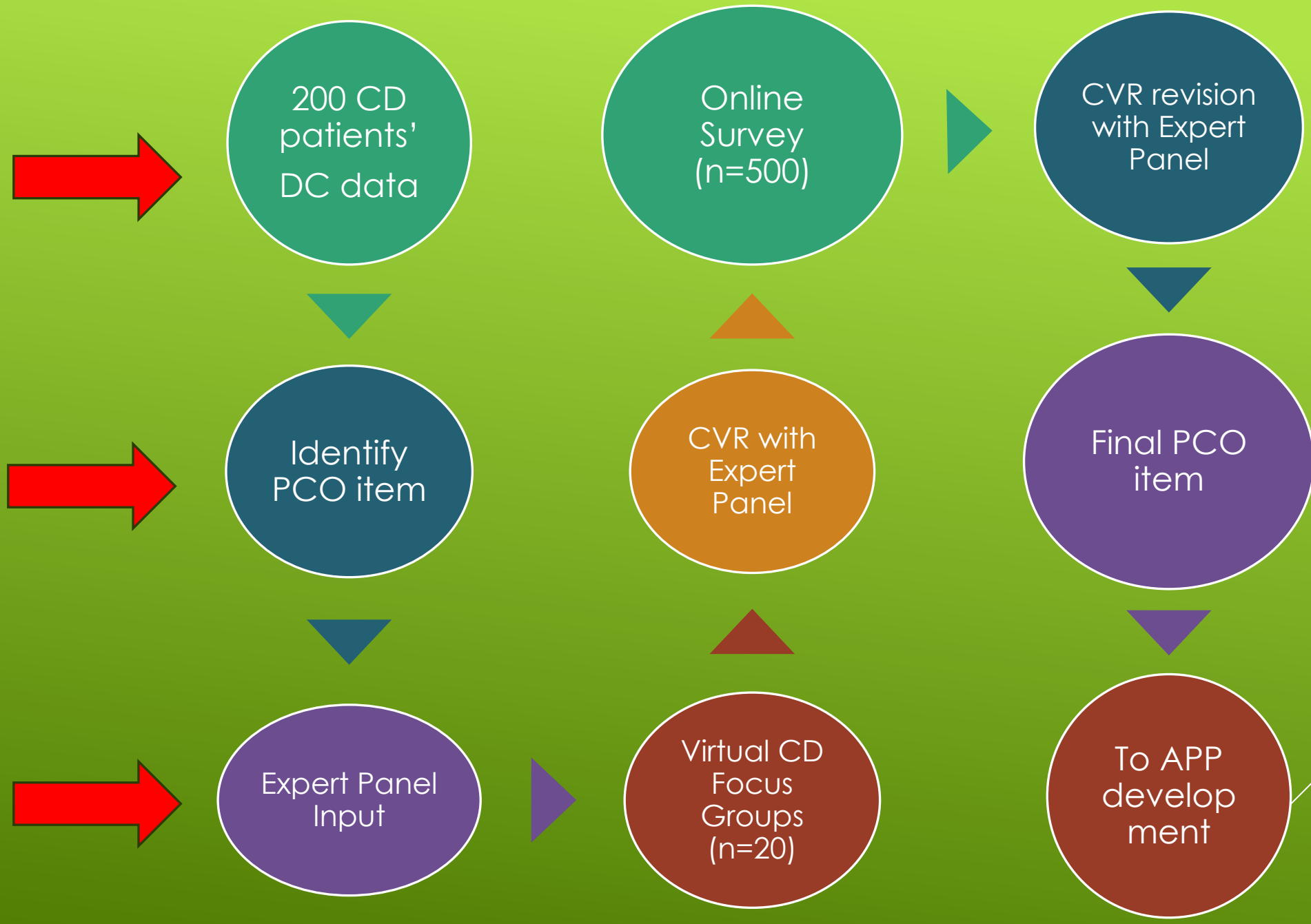
Benign Essential
Blepharospasm
Research Foundation

CD Panel	BSP Panel	LD Panel
Chair: Sarah Pirio Richardson MD	**Chair:** Brian Berman MD MS	**Chair:** Sarah Schneider MS SLP
NEUROLOGY	**OPHTHALMOLOGY**	**OTOLARYNGOLOGY**
Joseph Jankovic MD	Amanda Henderson MD	Adam Klein MD
Charles Adler MD	Andrew Harrison MD	Michael Pitman MD
Marina de Koning-Tijssen MD	**NEUROLOGY**	**NEUROLOGY**
Cynthia Comella MD	Gianni de Fazio MD	Charles Adler MD PhD
PHYSICAL THERAPY	Mark Hallett MD	Joel Perlmutter MD
Teresa Kimberly PhD PT	Joseph Jankovic MD	**SPEECH LANGUAGE PATHOLOGY**
PATIENT ADVOCACY GROUP	**PATIENT ADVOCACY GROUP**	Edie Hapner Phd CCC-SLP
Janet Hieshetter	Jane Boyd MD	**PATIENT ADVOCACY GROUP**
Monika Benson		Kimberly Kuman
STATISTICIAN	**STATISTICIAN**	**STATISTICIAN**
Fares Qeadan PhD	Fares Qeadan PhD	Fares Qeadan PhD
DC EXEC MEMBER	**DC EXEC MEMBER**	**DC EXEC MEMBER**
H.A. Jinnah MD PhD	H.A. Jinnah MD PhD	H.A. Jinnah MD PhD
DC PROGRAM MANAGER	**DC PROGRAM MANAGER**	**DC PROGRAM MANAGER**
Gamze Kilic-Berkmen PhD	Gamze Kilic-Berkmen PhD	Gamze Kilic-Berkmen PhD


200 CD patients' DC data
Online Survey (n=500)
CVR revision with Expert Panel
Identify PCO item
CVR with Expert Panel
Final PCO item
Expert Panel Input
Virtual CD Focus Groups (n=20)
To APP development

	ROUND 1	
ITEMS		EXCLUSIONS
1	Frustrated_	
2	Down_	
3	Upset_	
4	Depressed_	
5	Socialising_with_friends_of_fami	
6	Fed_Up_	
7	Enjoyment_of_social_situations_	
8	Aggravated_	
9	Stressed_	
10	Irritated_	
11	Scared_	
12	More_self_conscious_in_social_si	
13	Lack_of_confidence_	
	Angry_	OOB below zero
	Anxious_	OOB below zero
	Worried_	OOB below zero
	Impatient_	OOB below zero
	Fearful_	OOB below zero
	Less_relaxed_in_social_situation	OOB below zero
	Uneasy_talking_to_strangers_	OOB below zero
	Embarrassed_about_eating_in_publ	OOB below zero
	Annoyed_	OOB below zero
	Everybody_is_staring_at_you_	OOB below zero
	Embarrassed_going_out_in_public_	OOB below zero
	Lack_of_self_confidence_	OOB below zero

DYSTONIA COALITION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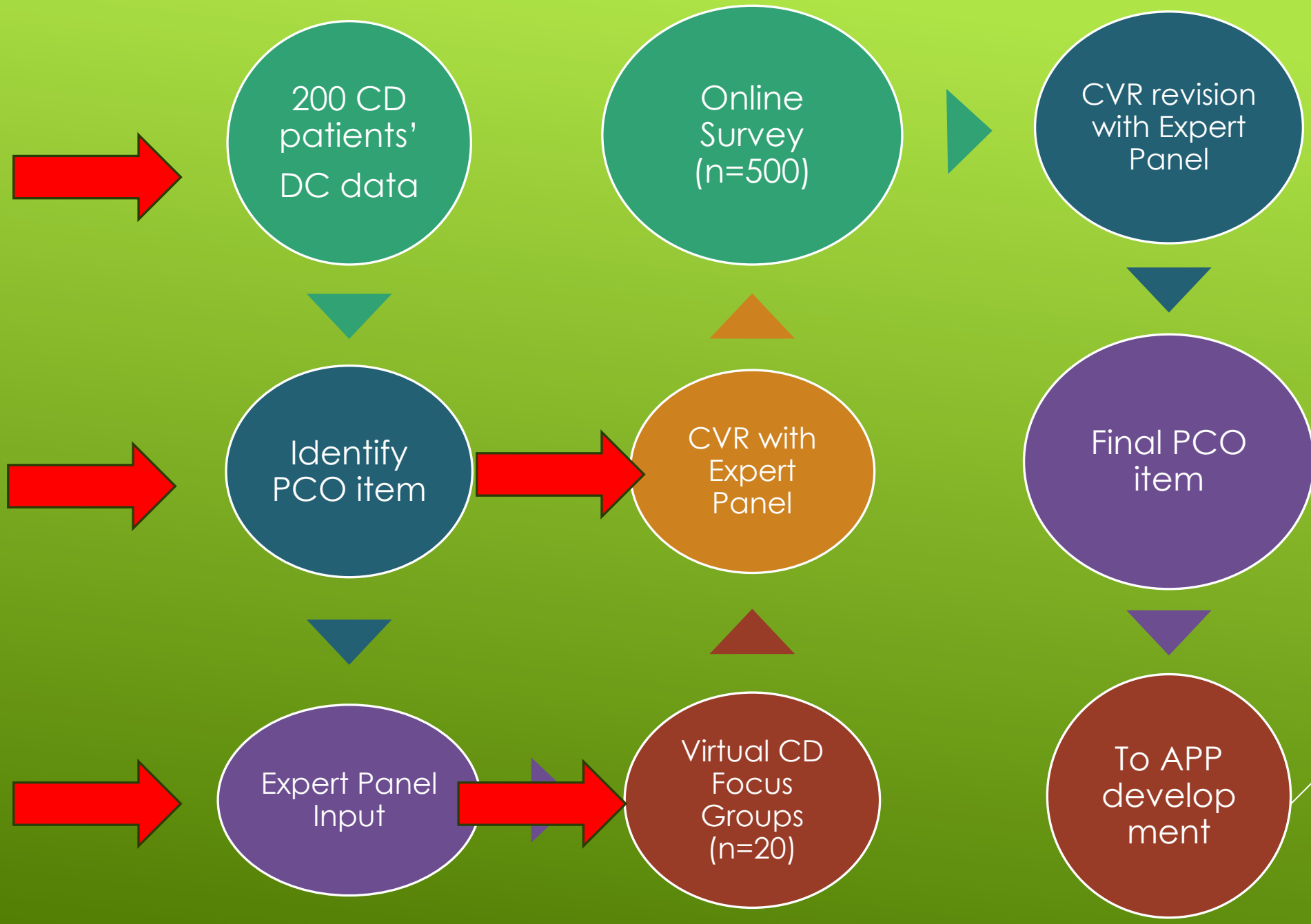
	ROUND 1		ROUND 2	
ITEMS		EXCLUSIONS		EXCLUSIONS
1	Frustrated_		Frustrated_	
2	Down_		Down_	
3	Upset_		Upset_	Repetitive/duplicate
4	Depressed_		Depressed_	Repetitive/duplicate
5	Socialising_with_friends_of_fami		Socialising_with_friends_of_fami	
6	Fed_Up_		Fed_Up_	Repetitive/duplicate
7	Enjoyment_of_social_situations_		Enjoyment_of_social_situations_	Repetitive/duplicate
8	Aggravated_		Aggravated_	Repetitive/duplicate
9	Stressed_		Stressed_	
10	Irritated_		Irritated_	Repetitive/duplicate
11	Scared_		Scared_	
12	More_self_conscious_in_social_si		More_self_conscious_in_social_si	Repetitive/duplicate
13	Lack_of_confidence_		Lack_of_confidence_	Repetitive/duplicate
	Angry_	OOB below zero		
	Anxious_	OOB below zero		
	Worried_	OOB below zero		
	Impatient_	OOB below zero		
	Fearful_	OOB below zero		
	Less_relaxed_in_social_situation	OOB below zero		
	Uneasy_talking_to_strangers_	OOB below zero		
	Embarrassed_about_eating_in_publ	OOB below zero		
	Annoyed_	OOB below zero		
	Everybody_is_staring_at_you_	OOB below zero		
	Embarrassed_going_out_in_public_	OOB below zero		
	Lack_of_self_confidence_	OOB below zero		

DYSTONIA COALITION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CD

SYMPTOMS DOMAIN

(For each item below please score in the Relevancy and Clarity columns from 1-4 using the Rating Key)

Item	Relevancy	Clarity
1. How much neck tightness or pulling do you have due to cervical dystonia?		
2. How much neck pain do you have due to cervical dystonia?		
3. Does your head twist or turn involuntarily due to cervical dystonia?		
4. How much shaking or tremor do you have in your neck or head due to cervical dystonia?		

BSP

Symptom Domain

1. How often do you blink too much?
   Never----------Always

2. How much difficulty do you have keeping your eyes fully open?
   None----------Extreme

3. How much discomfort do you have due any gritty, sandy or burning sensations in your eyes?
   None----------Extreme

4. Do spasms close your eyes against your will?
   None----------Always

5. How much discomfort do you have with bright light?
   None----------Always

6. How often do you experience uncontrollable movements of your tongue, mouth or jaw?
   Never----------Always

DYSTONIA COALITION

QUANTIFICATION OF CONTENT VALIDITY RATING: CD Expert Panel

TABLE 1: Rating Key for Expert Panel

Relevancy	Clarity
1 [not relevant]	1 [not clear]
2 [item needs some revision]	2 [item needs some revision]
3 [relevant but needs minor revision]	3 [clear but needs minor revision]
4 [very relevant]	4 [very clear]

DYSTONIA COALITION

Symptoms Domain										Number Agreement	I-CVI
SD Q1. Relevancy	4		3	4	4	4	4	4	4	8	1
SD Q1. Clarity	4		2	4	4	4	4	3	4	7	0.875
SD Q2. Relevancy	4		4	4	4	4	4	4	4	8	1
SD Q2. Clarity	4		4	4	4	3	3	3	4	8	1
SD Q3. Relevancy	4		3	4	4	4	4	4	4	8	1
SD Q3. Clarity	4		3	2	4	3	4	4	4	7	0.875
SD Q4. Relevancy	4		4	4	4	4	4	3	4	8	1
SD Q4. Clarity	4		4	4	4	3	4	3	4	8	1

DYSTONIA COALITION

ACTIVITIES DOMAIN

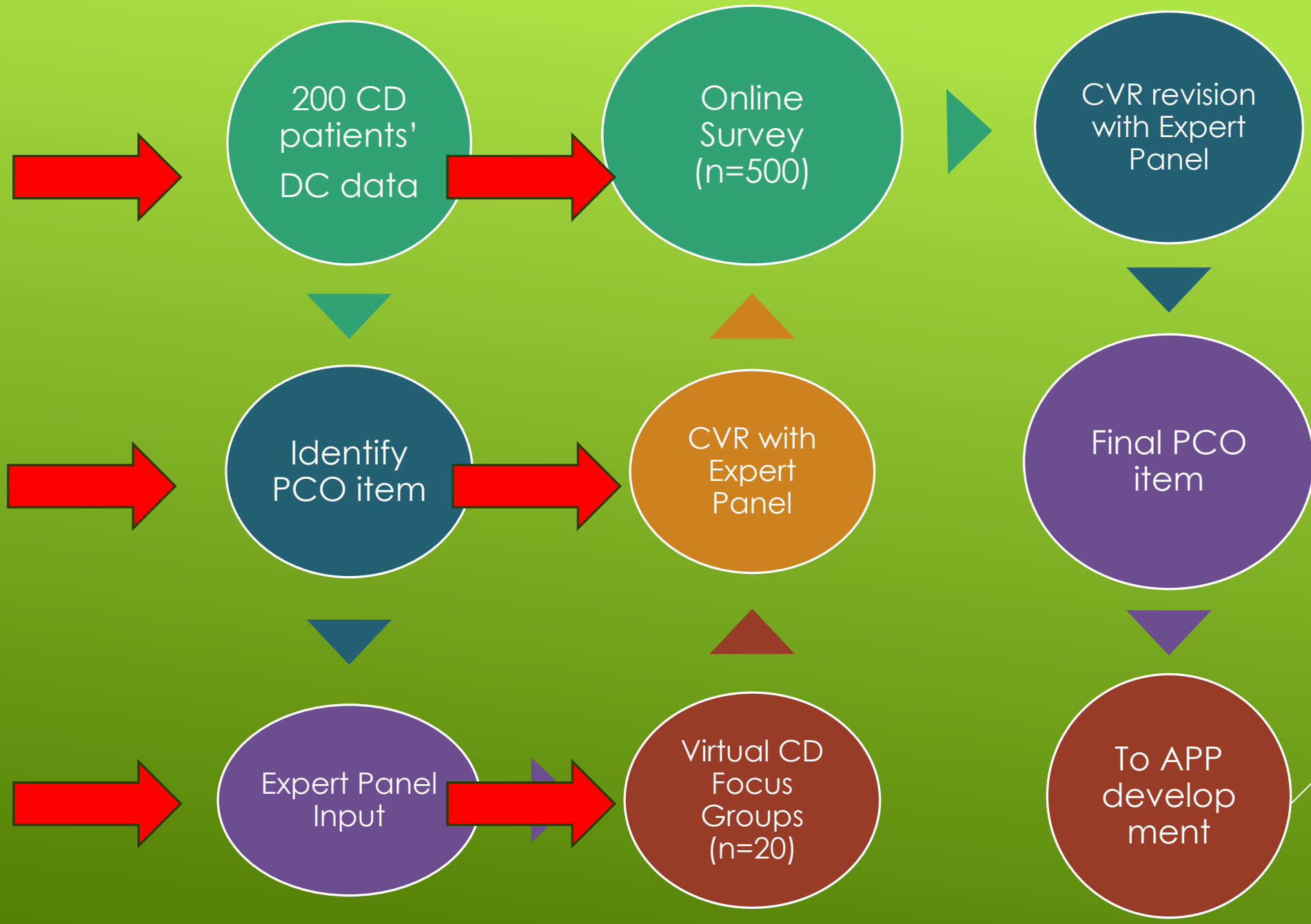
(For each item below please score in the Relevancy and Clarity columns from 1-4 using the Rating Key)

Item	Relevancy	Clarity
1. How much difficulty do you have in your activities of daily living (dressing, eating, bathing, writing) due to your cervical dystonia?		
2. How much limitation do you have in work performance (either household work or outside employment) due to your cervical dystonia?		
3. How much limitation do you have in driving due to your cervical dystonia?		
4. How much limitation do you have in exercising due to your cervical dystonia?		
5. How much limitation do you have in activities that require holding the head straight (such as using a computer or watching television) due to your cervical dystonia?		
6. How much limitation do you have in your leisure activities due to your cervical dystonia?		

DYSTONIA COALITION

Activities Domain										Number Agreement	I-CVI
AD Q1. Relevancy	4		4	4	4	4	4	4	4	8	1
AD Q1. Clarity	4		3	4	4	4	4	3	4	8	1
AD Q2. Relevancy	4		4	4	4	4	4	4	4	8	1
AD Q2. Clarity	4		3	4	4	4	4	4	4	8	1
AD Q3. Relevancy	4		3	4	4	4	4	4	4	8	1
AD Q3. Clarity	4		3	4	4	3	4	4	2	7	0.875
AD Q4. Relevancy	1		1	4	4	3	4	4		5	0.625
AD Q4. Clarity	4		1	2	4	3	4	3	2	5	0.625
AD Q5. Relevancy	4		4	4	4	4	3	3	4	8	1
AD Q5. Clarity	4		3	4	4	3	4	4	4	8	1
AD Q6. Relevancy	4		3	4	4	3	4	3	4	8	1
AD Q6. Clarity	4		3	4	4	3	4	3	2	7	0.875

DYSTONIA COALITION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Distribution of response by weeks:

week	Frequency	Percent	Cumulative Frequency	Cumulative Percent
June 22-June 26	99	16.78	99	16.78
June 27-July 3	303	51.36	402	68.14
July 4-July 10	84	14.24	486	82.37
July 11-July 15	104	17.63	590	100.00

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Question		Frequency	Percent of patients reported YES for relevance of question to their diagnosis of cervical dystonia	Rank
1	neck tightness or pulling	519	97.01	1
11	quality of life	437	95.83	2
2	neck pain	468	91.23	3
9	ability to do activities that require holding your head straight	424	91.18	4
13	ability to interact in social situations	397	89.01	5
10	ability to do leisure activities	408	88.50	6
3	twisting or turning	436	86.85	7
14	feeling anxious or depressed	379	85.75	8
8	ability to exercise	393	83.97	9
6	work performance	391	81.63	10
5	ability to do activities of daily living	374	77.11	11
12	sleep	343	75.88	12
4	shaking or tremor	363	73.63	13
7	ability to drive	344	72.27	14

Pirio Richardson et al., unpublished data

PCO DEVELOPMENT : CONCLUSIONS

- The development of these PCO measures was accomplished during the COVID-19 pandemic
  1) using robust existing patient-centered data from previous Dystonia Coalition projects
  2) active engagement with PAGs
  3) use of virtual focus groups and online surveys

DYSTONIA COALITION

APP DEVELOPMENT

DYSTONIA COALITION

Collaboration with TekSynap

Weekly meetings
iOS beta testing (through TestFlight)

Android beta testing (through Google Drive download)

Application Features

- User-friendly interface
- Easy-to-read text
- Simple questionnaire slider bar
- Menu toolbar
- Push-notification reminder switch

Data Storage

Web-based secure admin panel

Accessibility

iOS compatibility

Android compatibility

"SYMPTOM SNAP"

- 16 Cervical Dystonia questions
- 18 Blepharospasm questions
- 15 Laryngeal Dystonia questions
- Numerical rating scale format
- Sliding bar with anchors

DYSTONIA COALITION

DEVELOPMENT OF A SMARTPHONE APPLICATION ABLE TO CAPTURE PATIENT-CENTERED OUTCOME (PCO) MEASURES FOR DYSTONIA

Sarah Pirio Richardson, Paul Reyes, Arlann Erskine, Brian Berman, Sarah L. Schneider, Janet Hieshetter, Kimberly Kuman, Cynthia Comella, David Peterson, Gamze Kilic-Berkmen, Laura Wright, Fares Qeadan, Samantha Pentecost, Joel S. Perlmutter, H. A. Jinnah

INTRODUCTION

GOAL

To establish clinical trial readiness for novel treatments for dystonia.

BACKGROUND AND STAGE A: PCO DEVELOPMENT

Botulinum neurotoxin (BoNT) is a first-line therapy for focal dystonia resulting in significant improvement, yet 1/3 of patients discontinue use suggesting that the therapy may not fully address patient expectations. Patient-Centered Outcome (PCO) measures for three major dystonia subtypes – cervical dystonia (CD), blepharospasm (BSP), and laryngeal dystonia (LD) – across motor, disability, and psychosocial domains were developed.

STAGE A: APP DEVELOPMENT

Develop a smartphone application able to capture PCO measures to track changes in responses over time.

METHODS

Collaboration with software company TekSynap

- Weekly meetings with developers
- iOS beta testing (through TestFlight)
- Android beta testing (through Google Drive download)

RESULTS

Application Features

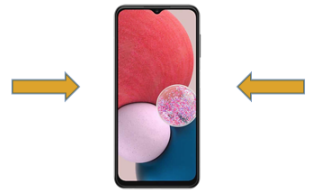
- User-friendly interface
- Easy-to-read text
- Simple questionnaire slider bar
- Menu toolbar
- Push-notification reminder switch

Pages

- Introduction Page
- Login Page
- Home Page
- Questionnaire Pages
- Contact Us Page
- Notification Page

RESULTS

TEST THE APP



TEST THE APP

RESULTS

Questionnaires

- 16 Cervical Dystonia questions
- 18 Blepharospasm questions
- 15 Laryngeal Dystonia questions
- Numerical rating scale format

Data Storage

- Web-based secure admin panel

Accessibility

- iOS compatibility
- Android compatibility

CONCLUSIONS

NEXT STEPS

Stage B: Project Recruitment

- Invite patients regularly receiving BoNT as part of their standard clinical care to install the app on a smartphone and complete the questions in the app on a weekly basis throughout their BoNT cycle
- Use app data to measure therapeutic response to BoNT on a weekly basis

Future Application/Data Uses

- Application used as a journal for users to record their symptoms
- Data used to provide direction in development of novel treatments for dystonia

REFERENCES AND ACKNOWLEDGEMENTS

Kilic-Berkmen G, et al. The Dystonia Coalition: A Multicenter Network for Clinical and Translational Studies. *Front Neurol.* 2021;12(660909)

DYSTONIA MEDICAL RESEARCH FOUNDATION

DYSPHONIA INTERNATIONAL
FORMERLY NATIONAL SPASMODIC DYSPHONIA ASSOCIATION

Benign Essential Blepharospasm Research Foundation

DYSTONIA COALITION

RARE DISEASES CLINICAL RESEARCH NETWORK

THE UNIVERSITY OF NEW MEXICO

DYSTONIA COALITION

PCO VALIDATION

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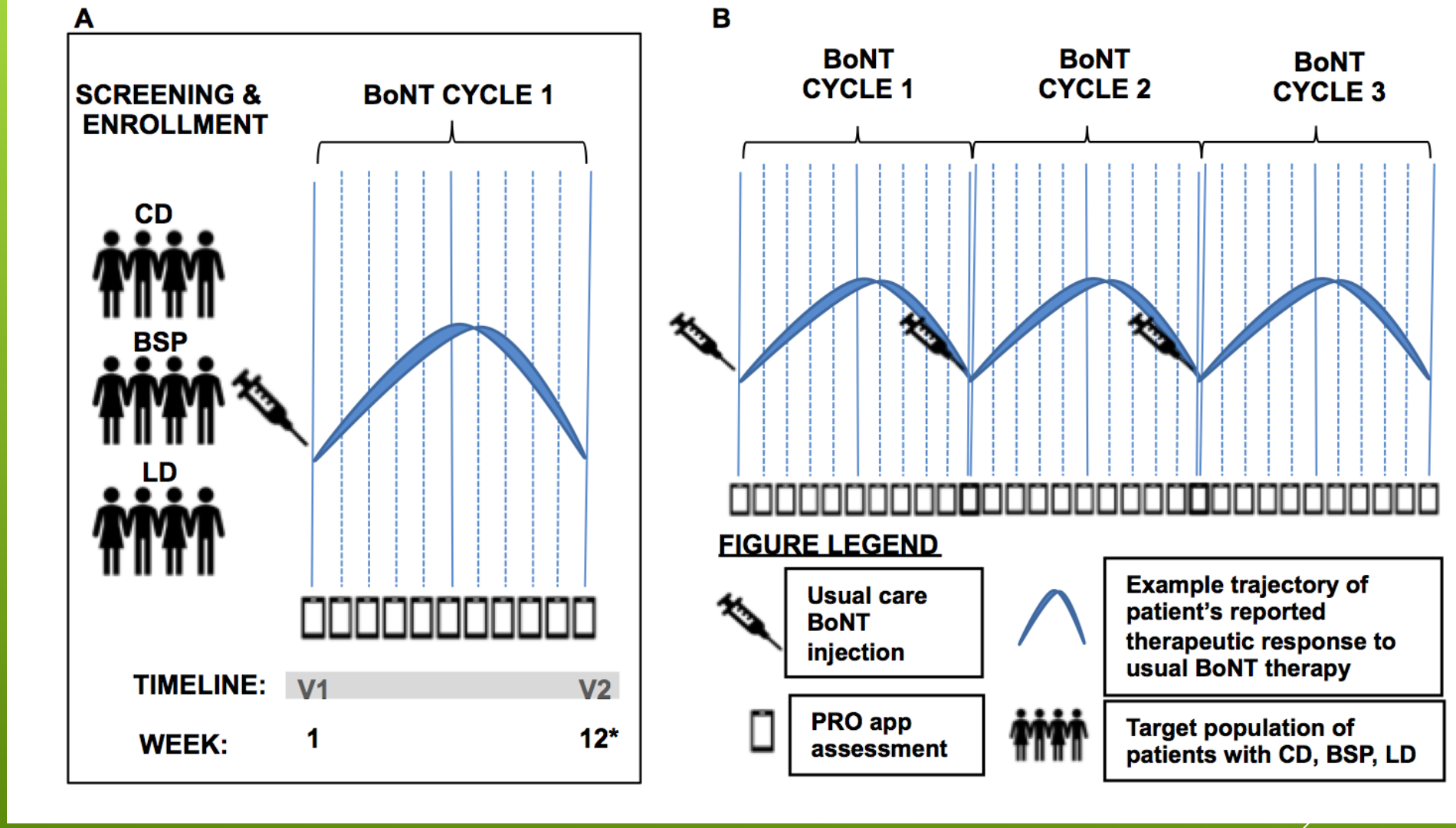
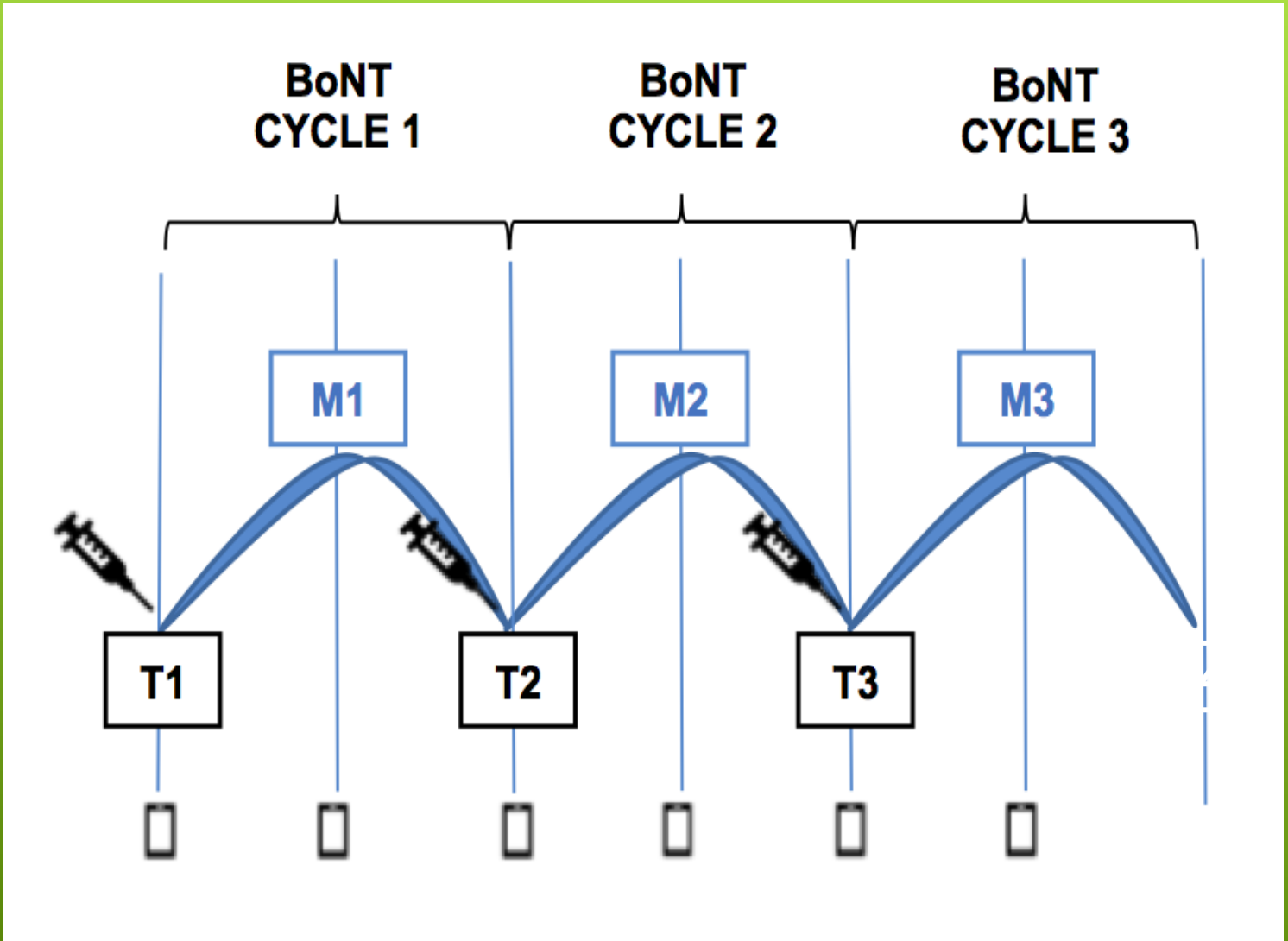


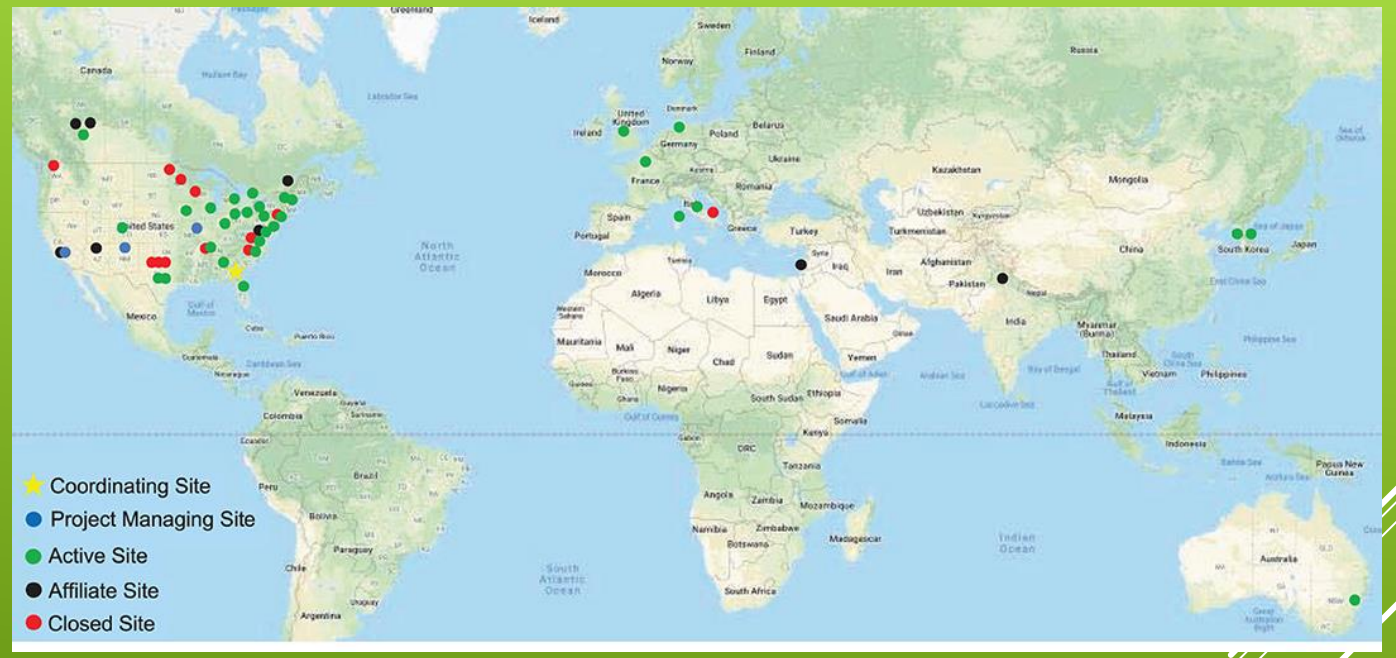
DYSTONIA COALITION



ENROLLMENT GOAL:
80 CD
80 BSP
80 LD
(CEILING 100)

DYSTONIA COALITION

- Sites were chosen based on interest in participating and track record of successful enrollment in prior DC funding cycles
- Active site
  - IRB-approved
  - Site activated by DC
  - MOU with DMRF
- English-speaking



SITE ACTIVATION PROCESS

Kilic-Berkmen et al. Front. Neurol., 08 April 2021 | https://doi.org/10.3389/fneur.2021.660909

DYSTONIA COALITION

- Baylor
- Emory
- *Rochester*
- Rush
- Toronto Western
- U Calgary
- U Cincinnati
- Colorado Anschutz
- U Florida
- U Iowa
- U New Mexico
- *U Maryland*
- VCU
- WashU
- *Westmead Hospital*

Kilic-Berkmen et al. Front. Neurol., 08 April 2021 | https://doi.org/10.3389/fneur.2021.660909

PCO coordinator:
Paul Reyes
University of New Mexico

PCO Coordinator:
Arlann Erskine
University of New Mexico

- Each PCO recruiting site will have 4 months (from the start day of the project) to enroll 10 cervical dystonia, 10 blepharospasm, and 10 laryngeal dystonia patients

- Once the 4-month period is over, recruitment will become competitive, and any PCO site can recruit until total targets are reached as long as <25% total n

- The aim is to complete enrollment of all 100 cases of each subtype (CD, BSP, LD) within 6 months of project start date, and then follow each case over 3 injection cycles

PCO RECRUITING QUOTA

DYSTONIA COALITION

- ✓ Attend or review recorded PCO Investigator and Coordinator Training
- ✓ Obtain APP access and training (to be coordinated by UNM Site)
- ✓ Receipt of revised Study Manual and all PCO CRFs (to be coordinated by UNM Site and Emory)

SITE ACTIVATION PROCESS

FUTURE DIRECTIONS

DYSTONIA COALITION

- Use as an outcome measure in clinical trials
- Allow the identification of therapeutic gaps
  - Comparison to clinician rating scales and objective measures
- Diary function

?

DYSTONIA COALITION

NIH/NCATS/NINDS U54 NS116025

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