Clinical trials for dystonia

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What is important to patients

1. Optimal treatment options
   - A. BoNT: some not responsive
   - B. Oral meds: undesirable side effects
   - C. Surgery: some hesitant

2. Insurance issues

3. Finding the right specialist

Our focus: measuring motor severity … why do we care?

- All in the service of improved treatment…

- Long term: Human research on mechanisms
  - (do the -omics, imaging, neurophys, etc. correlate with motor severity?)

- Short term: Trial outcomes

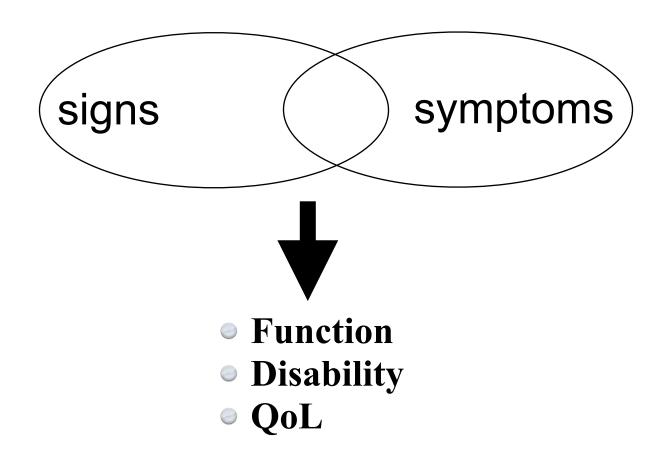# Pivotal to trial outcomes: measuring SEVERITY

before

intervention
(meds, BoNT, DBS, TMS, PT, placebo, etc.)

after

1. Compare before and after
   (e.g. TWSTRS(before) - TWSTRS(after))

2. After intervention, assay "change"
   (e.g. PGI-C)

Measuring severity of WHAT?

signs | symptoms

- **Function**
- **Disability**
- **QoL**

(i.e. *concept(s) of interest* (COI))

Measuring severity: HOW/WHO?

FDA categories of *clinical outcome assessments* (COAs) based on **WHO** is doing the measuring:

- ClinRO: **clinician** reported outcome
  - (i.e. clinical rating scales)

- ObsRO: **observer** reported outcome
  - (someone other than health professional or patient)

- PRO: **patient** reported outcome
  - (a.k.a. patient centered outcomes, PCOs)

Rating scales are subjective

- ClinRO: **clinician** reported outcome
- ObsRO: **observer** reported outcome
- PRO: **patient** reported outcome

} all based on *__human__* judgment

- • Human judgment is intrinsically **subjective**

  - • Affected by training, experience, etc.
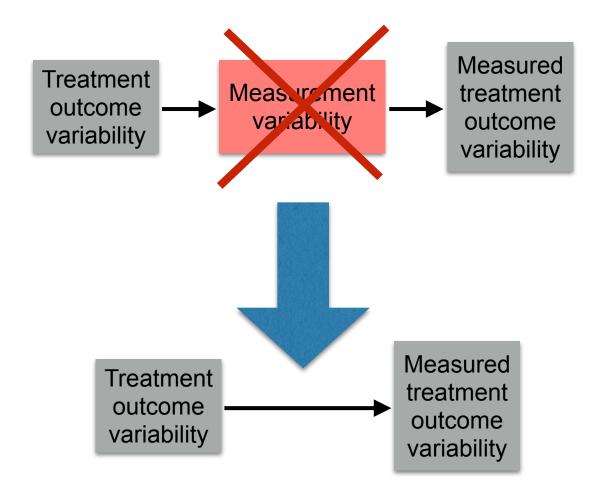
  - • Not necessarily wrong, just highly **variable**

The variability of subjective measures has consequences

- It gets conflated with treatment outcome variability:

```
┌────────────┐      ┌──────────────┐      ┌────────────┐
│ Treatment  │      │ Measurement  │      │ Measured   │
│ outcome    │ ───► │ variability  │ ───► │ treatment  │
│ variability│      │              │      │ outcome    │
│            │      │              │      │ variability│
└────────────┘      └──────────────┘      └────────────┘
```

- Variability reduces intra- and inter-rater reliability
    - Within individual trials
        - Intra-rater: before / after treatment
        - Inter-rater: multi-site trials
    - Across different trials
        - Meta analyses
- Variability decreases statistical power, thereby requiring higher Ns (and trial costs), longer delays, higher risk

What if we could circumvent the variability of subjective measures?

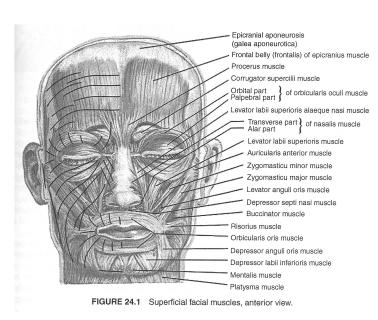# OBJECTIVE measures: definitions

How do we define "objective"?: each measurement does **not** depend on human judgement
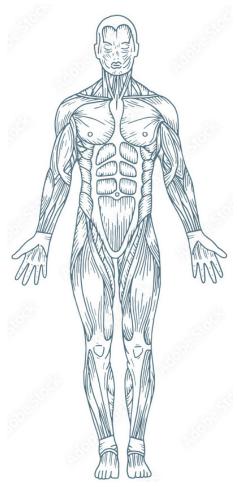
Terminology can be problematic:

- "technology-based objective measures" (TOMs, Espay 2016 Mov Disord; to distinguish from subjective methods labeled as "objective"?)

- "digital methods"

  - e.g. "digital health technology" (FDA)
  - *but* digital implementations of subjective measures, e.g. "electronic CRSs"; apps being developed for PROs, etc.)
  - how about a ruler?

Objective measures for dystonia

- kinematics
  - optical,
  - reflective, and/or
  - electromagnetic markers
- IMUs (inertial measurement units)
  - accelerometers
  - gyroscopes
- EMG
- Video
  - 3d/depth
  - 2d

Epicranial aponeurosis
(galea aponeurotica)
Frontal belly (frontalis) of epicranius muscle
Procerus muscle
Corrugator supercilii muscle
Orbital part } of orbicularis oculi muscle
Palpebral part }
Levator labii superioris alaeque nasi muscle
Transverse part } of nasalis muscle
Alar part }
Levator labii superioris muscle
Auricularis anterior muscle
Zygomasticu minor muscle
Zygomasticu major muscle
Levator anguli oris muscle
Depressor septi nasi muscle
Buccinator muscle
Risorius muscle
Orbicularis oris muscle
Depressor anguli oris muscle
Depressor labii inferioris muscle
Mentalis muscle
Platysma muscle

FIGURE 24.1 Superficial facial muscles, anterior view.
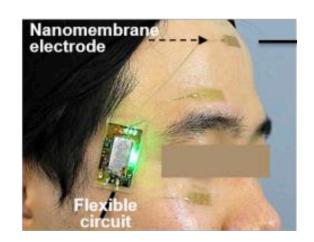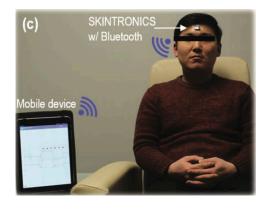
"Wearables" are becoming less obtrusive

Soft Nanomembrane Sensors and Flexible
Hybrid Bioelectronics for Wireless
Quantification of Blepharospasm

Musa Mahmood, Shinjae Kwon, Gamze Kilic Berkmen, Yun-Soung Kim, Laura Scorr, H. A. Jinnah
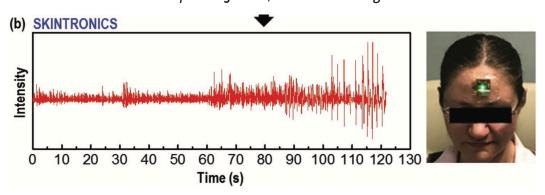and Woon-Hong Yeo, *Senior Member*, IEEE

FULL PAPER

Flexible Electronics

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Soft Material-Enabled, Active Wireless, Thin-Film Bioelectronics for Quantitative Diagnostics of Cervical Dystonia

Young-Tae Kwon, Yongkuk Lee, Gamze Kilic Berkmen, Hyo-Ryoung Lim, Laura Scorr, Hyder A. Jinnah, and Woon-Hong Yeo*

So let's look at clinical trials ….
… and see what measures they have used

Our approach to objective measures: video

Advantages of Video
(vs. IMUs, EMG, etc.)

- Clinical utility
  - Pervasive in movement disorders
  - Minimal additional resource requirements
    - equipment
    - expertise
    - time

- Less physically obtrusive
  (vs. markers, EMG electrodes, etc.)
  - minimizes observer effect!

- Enables telehealth, remote access, more frequent assays during ADLs

AI DOOMSDAY

Runaway AI Is an Extinction Risk, Experts Warn

A new statement from industry leaders cautions that artificial intelligence poses a threat to humanity on par with nuclear war or a pandemic.

WILL KNIGHT

05.30.23 09:05 AM

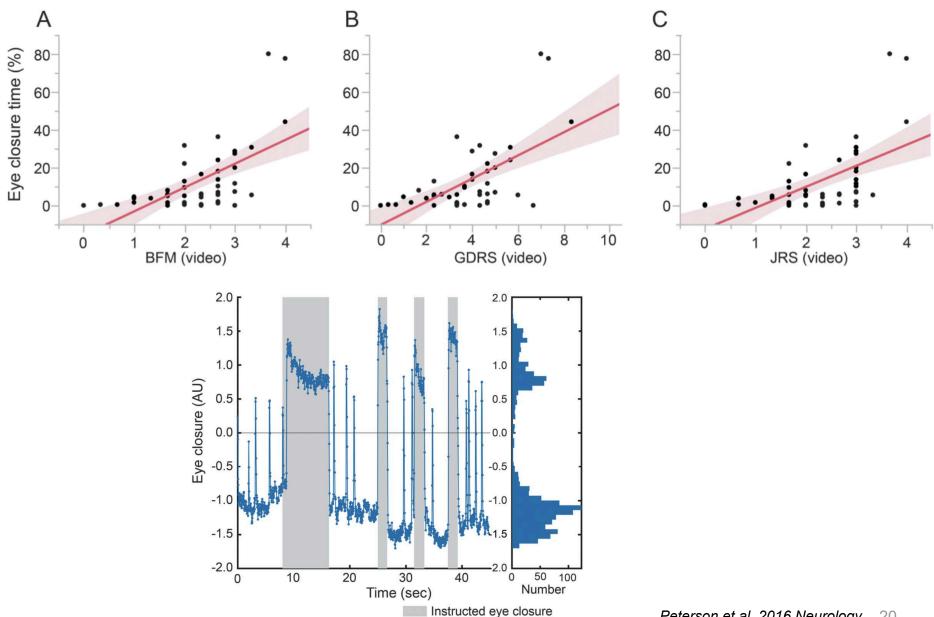# Analyzing videos with computer vision (instead of human vision)

Overall Approach:

- Develop software…
  - … the Computational Motor Objective Rater (**CMOR**)
  - … that leverages advances in AI (e.g. computer vision and machine learning/deep learning)

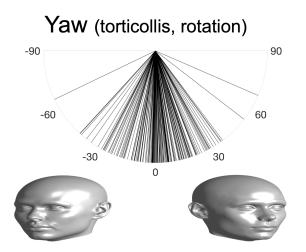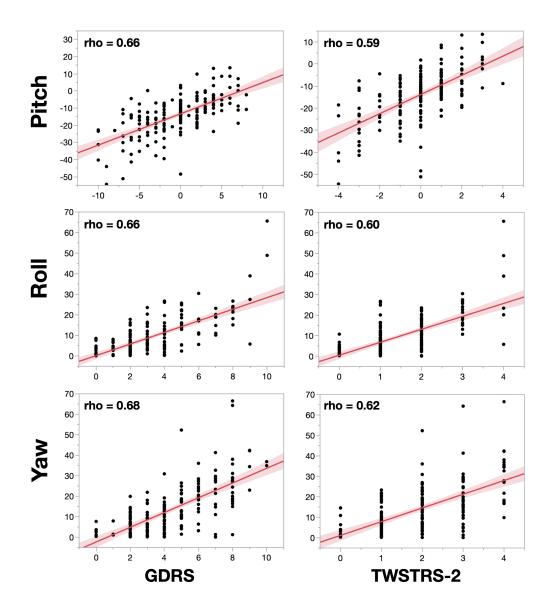- Test CMOR's convergent validity with clinical ratings severity

Scope:

- BSP and CD: videos from clinical exam

- LD: videos from laryngoscopic exam
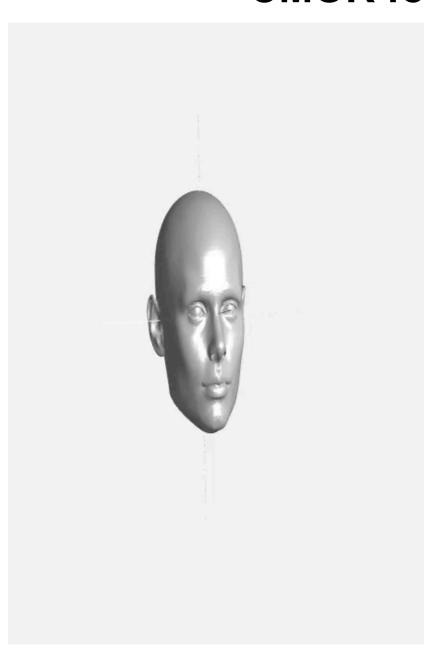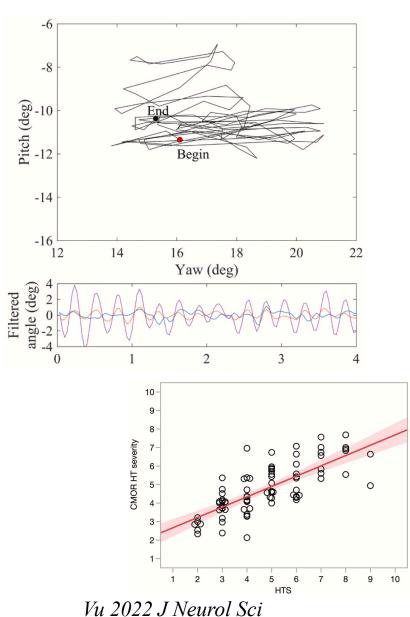
CMOR for eye closure in BSP

Instructed eye closure
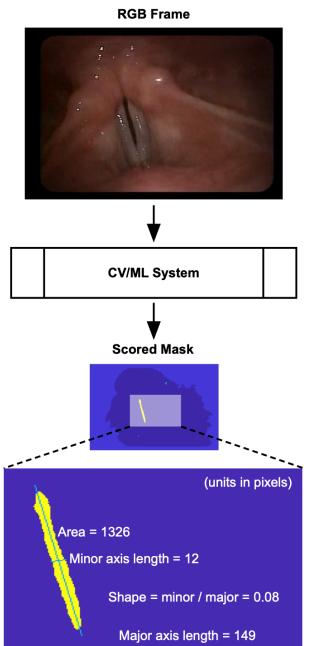
CMOR for CD: head deviation

Zhang 2022 Annals Clinical Translational Neurology

CMOR for CD: head tremor

Vu 2022 J Neurol Sci

CMOR for glottal dynamics in LD

RGB Frame

CV/ML System

Scored Mask

(units in pixels)

Area = 1326

Minor axis length = 12

Shape = minor / major = 0.08

Major axis length = 149

Can we predict ADSD voice quality by extracting glottal geometry from laryngoscopic video recordings?

How do dynamic features in the geometry of the glottis relate to voice quality in ADSD ?

Peterson et al. 2022 J Speech Lang Hear Res

Objective measures in a BSP trial

- Addex Pharmaceuticals

  - Allosteric modulators (AMs) for several CNS indications

  - dipraglurant: mGlu5 negative allosteric modulator (NAM)
    - PD LIDs

  - exploratory Phase 2 PCT in BSP
    - with the current IR formulation
    - assessments include clinical ratings, PROs, and objective measures:
      - CMOR and Skintronics

- *ClinicalTrials.gov Identifier: NCT05027997*
- https://www.addextherapeutics.com/en/pipeline/researches/dipraglurant-dystonia/
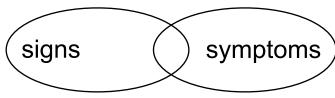
Measuring severity: the patient perspective

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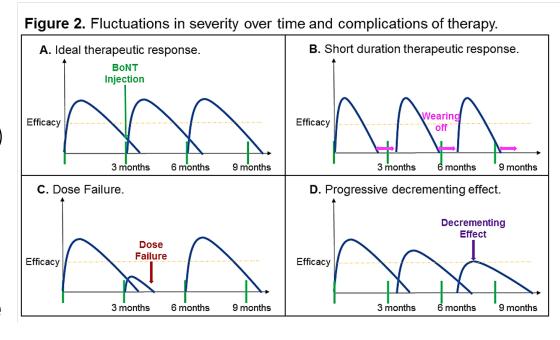 - (a.k.a. patient centered outcomes, PCOs)

Combine PRO's *and* Video-based objective measures

- BOTH enable measurement outside the clinic
  - Greater frequency
  - At home, in daily life settings
  - Patient-centered

- Synergies

signs ⟷ symptoms

In *context of use* involving BoNT cycles, we need more frequent measures

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

A. Ideal therapeutic response.
BoNT Injection
Efficacy
3 months   6 months   9 months

B. Short duration therapeutic response.
Efficacy
Wearing off
3 months   6 months   9 months

C. Dose Failure.
Efficacy
Dose Failure
3 months   6 months   9 months

D. Progressive decrementing effect.
Efficacy
Decrementing Effect
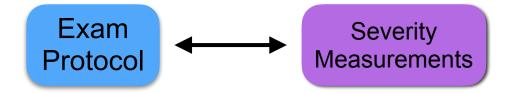3 months   6 months   9 months

Pirio Richardson and Jinnah 2019 Expert Opinion Drug Discovery

All assessments depend on the "tasks"

we need to be careful about **WHAT** is happening **during** the measurements (part of the COU ?)

especially for the dystonias; the moment-to-moment motor features depend on:

- sensory input
- attention
- task

Exam Protocol ⟷ Severity Measurements

one FDA clinical outcome assessments (COA) category:
- PerfO: performance outcome
  - based on "standardized task(s) according to a set of instructions"

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2. Insurance issues

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Collaborators and Sponsors

Buz Jinnah, Emory

Joel Perlmutter and Jo Wright, WUSTL

Mark Hallett, NINDS

Giovanni Defazio, Antonella Macerollo U Bari

Marni Bartlett, Apple

Terry Sejnowski CNL, Salk

Jake Whitehill, Worcester Polytechnic

Cindy Comella, Glenn Stebbins Rush University Medical Center

Brian Berman, VCU

DMRF

Dystonia Coalition

NIH NCATS (U54-NS11602)

RARE DISEASES
CLINICAL RESEARCH NETWORK

Benign Essential Blepharospasm Research Foundation

Dysphonia International

DoD CDMRP

CDMRP
Department of Defense

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Thank you

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