How to Design a Clinical Trial in COVID-19 Times

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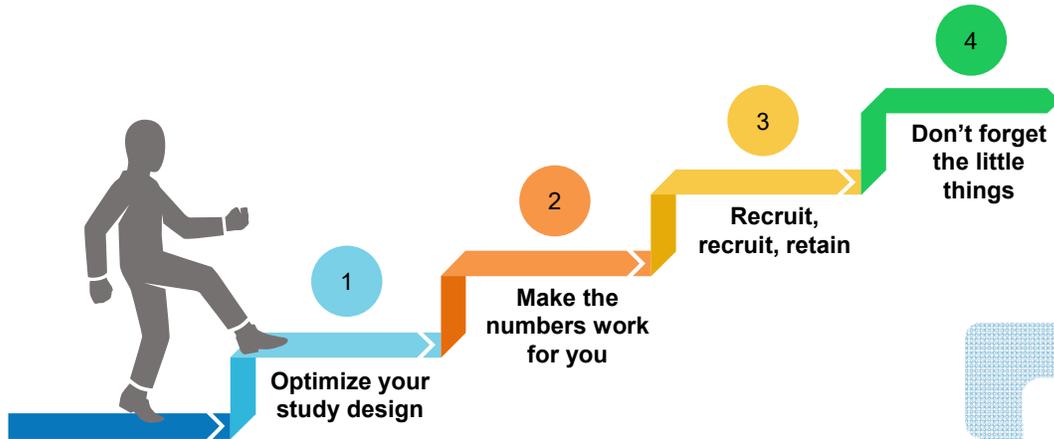*Cleveland Clinic, Cleveland, Ohio, USA*
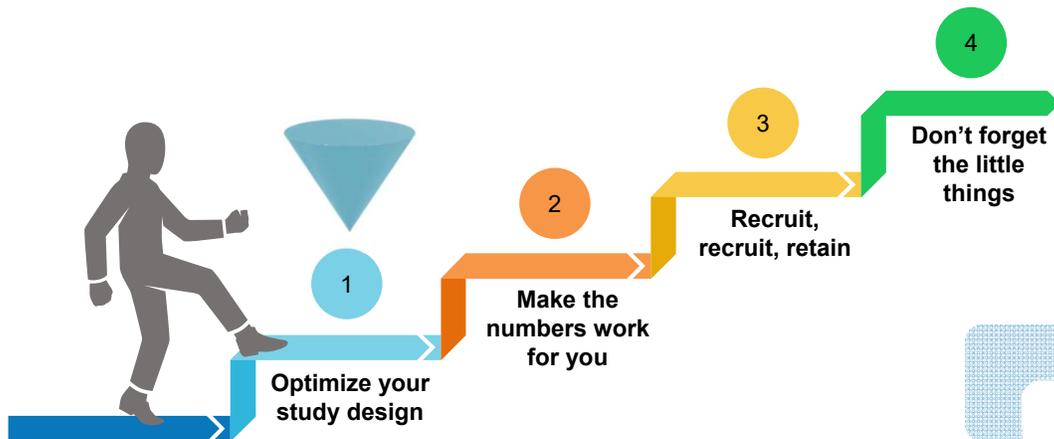
OBJECTION!

RELEVANCE?
memegenerator.net

DANGER

Irrelevant Content Ahead

It's not over till it's over

History repeats itself

Surviving a pandemic

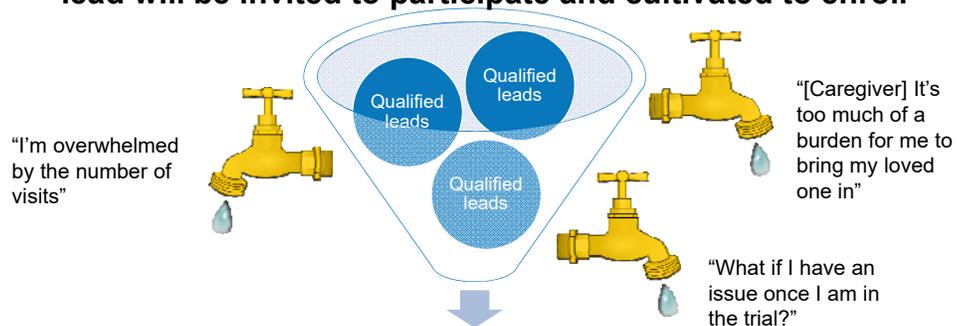# Surviving a pandemic: Clinical Trial Vaccine #1

Always apply the KISS principle

CONVERSION OF QUALIFIED LEADS

The most ignored step in recruitment is how a qualified lead will be invited to participate and cultivated to enroll

"I'm overwhelmed by the number of visits"

Qualified leads

Qualified leads

Qualified leads

"[Caregiver] It's too much of a burden for me to bring my loved one in"

"What if I have an issue once I am in the trial?"

Focusing on conversion strategies will be especially critical in dealing with a PD population

The Michael J. Fox Foundation for Parkinson's Research

Known conversion challenges

↓ Rigorous protocol
  - ↓ Extensive assessments and frequent site visits are a challenge, especially for PD patients in later-stage of disease and their caregivers

↓ Fragility of PD patient
  - ↓ Patients and their caregivers will be wary of disruption to their usual routine and having to change their regimen

↓ Caregiver burden
  - ↓ Caregivers will need to be bought-in to encourage trial participation, and to participate alongside PD patient

The Michael J. Fox Foundation for Parkinson's Research

Technology-based outcome measures to the rescue!

Patient
Mobile Device
Clinician
Caregiver
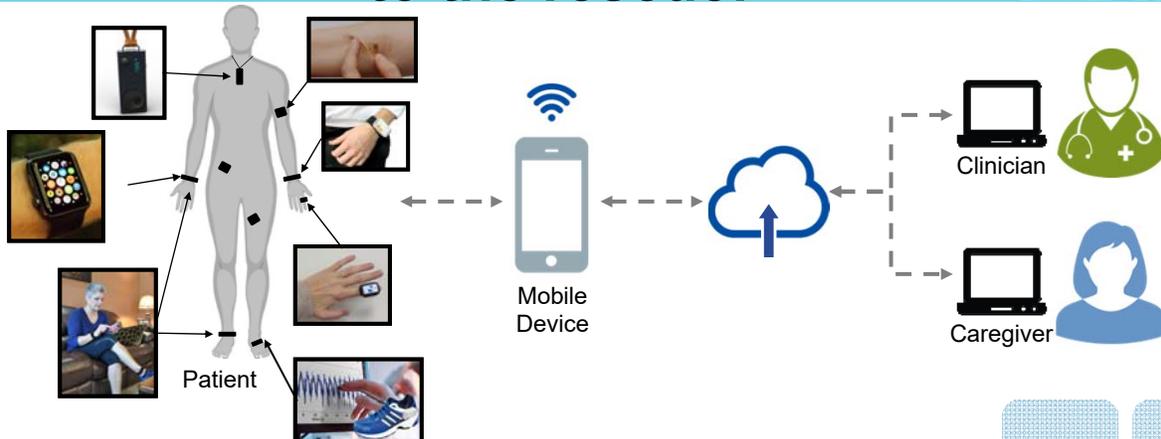
Adapted from Espay AJ, *et al.* (2016) Mov Disord, 1272-1282.
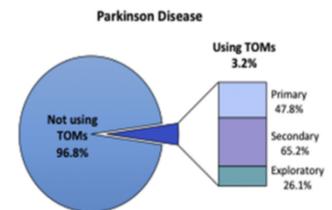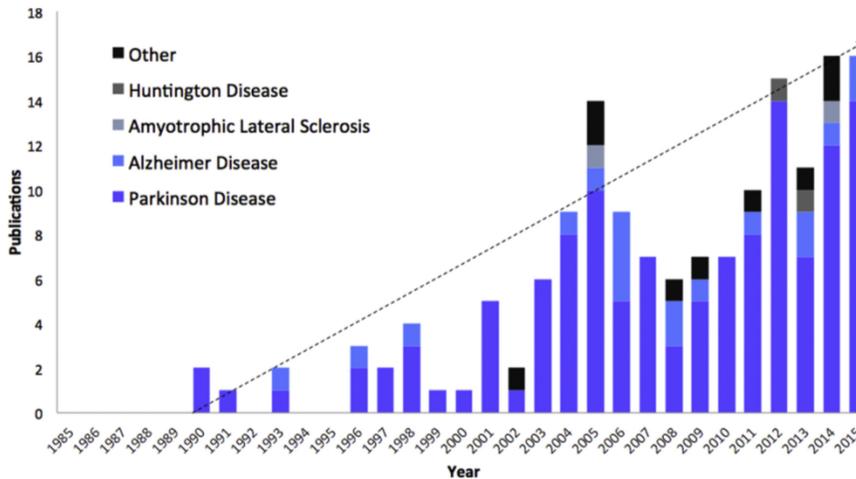
Patient-Centered Digital Outcome Measures

- 310.4 million wearable devices sold (2017)
- $30.5 billion revenue in the U.S. from wearable technology (2017)
- 504.6 million wearable devices to be sold (2021)

Clinical trials and technology-based outcomes

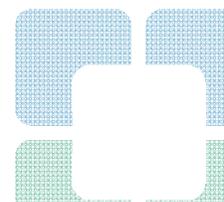C.A. Artusi et al. / Parkinsonism and Related Disorders 46 (2018) S53–S56

Challenges of technology-based outcome measures

Technology in Parkinson's Disease: Challenges and Opportunities

- Standardized development and validation processes
- Integration of devices from different companies in a comprehensive data platform
- Streamline regulatory approval of health technologies
- Challenging the effort, cost, and the risk of 'failure' of novel outcomes in clinical trials
- Patient engagement
- Provider engagement (clinical vs. technical know-how)
- Ethical and legal issues

Can there be too many gadgets? Or too much data?

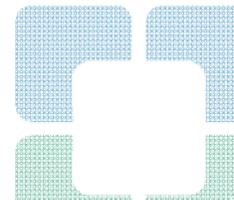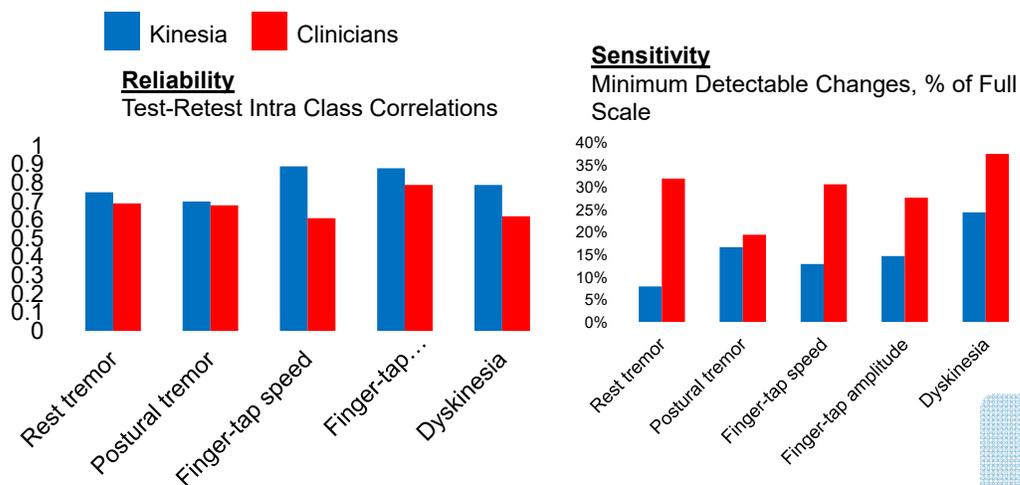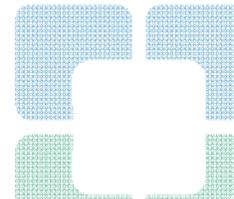# Kinesia wearable sensors

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More Reliable and Sensitive

D. Heldman, A. Espay, P. Lewitt, and J. Giuffrida (2014) Clinician Versus Machine: Reliability and Responsiveness of Motor Endpoints in Parkinson's Disease. *Parkinsonism Relat Disord.* 20(6):590–5.
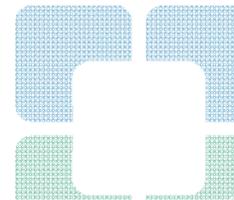
Faster and Less Expensive

- Higher sensitivity and reliability allows results with smaller number of patients
- Based on a published DBS study to evaluate constant-current safety and efficacy, 136 patients were required using clinician subject scores[1]
- Using objective measures, 18% less, or 25 fewer subjects could have been used
- With an average of $150k/subject, that is a $3.8M savings per study

Task	Placebo % change	Treatment % change	Number of Subjects based on Kinesia	Number of Subjects based on Clinician
Finger-tapping Speed	10	20	6	19
Finger-tapping amplitude	10	20	5	19
Finger-tapping rhythm	10	20	7	42
Postural Tremor	10	20	52	185
Rest Tremor	10	20	16	14
Toe-taps	10	20	4	10
Leg-Lifts	10	20	10	35
Gait	10	20	11	15

Patient Survey Responses

- Strongly Agree or Agree
- Neutral
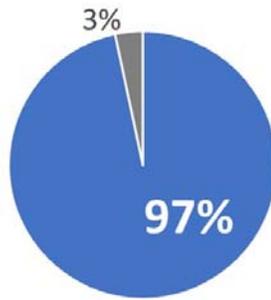- Strongly Disagree or Disagree

32 Patients at Cleveland Clinic Used Kinesia ONE in the Clinic and at Home for 2 weeks all day

3%
97%
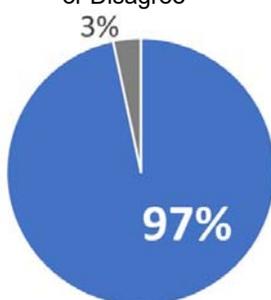
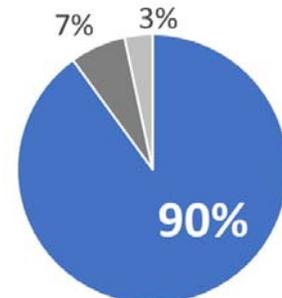The system was easy to set up - **97%**

3%
97%

Starting the app on the tablet was easy and straight-forward – **97%**
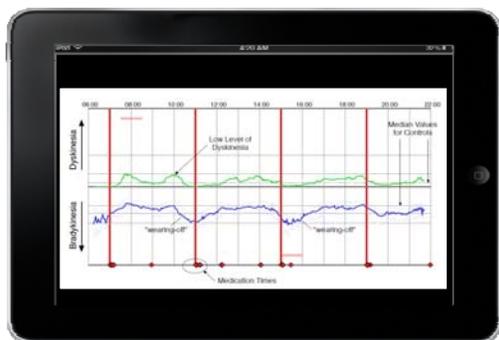
100%

It was easy to navigate through the assessments – **100%**

7% 3%
90%

I would use this system if recommended by my doctor – **90%**

The PKG System

TGA ✓ — Class I & Class IIa registered

CE ✓ — Class I, Class IIa & MHRA registered

FDA ✓ — Clearance to market

- A data logger
  - Tailored for PD
  - Digital accelerometry
  - Memory and battery for > 10 days
  - Vibration reminder for medication
- Proprietary mathematical algorithms
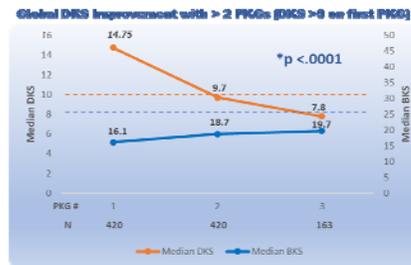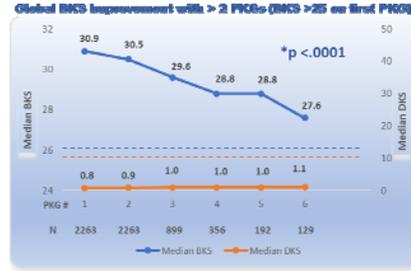 - Algorithm/data located in cloud
- Clinically relevant output

PKG Detects Complications
Not Identified by Standard Care

Study	Patients (n)	Detection of Complications of Therapy
Victoria (AUS)	28	• **12%** reported **dyskinesia** • **3%** reported **Impulsive Control Disorder**
Tasmania (AUS)	103	• Of 33 completing study & outside targets: • **82%** (27) treated for **bradykinesia/wearing off** • **15%** (5) for **dyskinesia/fluctuations** • 3% (1) for freezing of gait
UCSD (US)	28	• Symptoms detected by PKG at Visit 1; Visit 2: • **On-off fluctuations: 21.4%; 25%** • **Dyskinesia: 25%; 28.6%**
UCI/UCLA (US)	63	• Symptoms reported by PKG alone and not by subject: • **Dyskinesia: 33%** • **Tremor: 17%**
Parkinson's Institute (US)	89 (112 surveys)	• In 36 cases found new and precise information on **daily OFF time found 50% of time**

PKG Measures Symptom Improvement

- Large database study of > 27K PKGs from 2012-2018
- Sub-analysis of PKGs for subjects who had 2+ PKGs:
  - Bradykinesia: Significant changes in bradykinesia score from 1st to 2nd-6th PKGs (all p<0.0001)
  - Dyskinesia: Significant changes in dyskinesia score from 1st to 2nd & 3rd PKGs (both p<0.0001)

Lynch P, Pahwa R, Bergquist F, Horne M. Continuous Objective Monitoring in Parkinson's Disease: A description of over 25,000 Parkinson's symptom scores across the world using the Personal KinetiGraph (PKG) wearable monitoring device. AAN 2019 Abstract. http://indexsmart.mirasmart.com/AAN2019/SearchResults.php?Topic=&Session_Name=&Author=Lynch%2C+Peter%3Csup%3E1%3C%2Fsup%3E&Title=

Global BKS Improvement with > 2 PKGs (BKS >25 on first PKG)

*p <.0001

PKG #	1	2	3	4	5	6
Median BKS	30.9	30.5	29.6	28.8	28.8	27.6
Median DKS	0.8	0.9	1.0	1.0	1.0	1.1
N	2263	2263	899	356	192	129

Global DKS Improvement with > 2 PKGs (DKS >9 on first PKG)

*p <.0001

PKG #	1	2	3
Median DKS	14.75	9.7	7.8
Median BKS	16.1	18.7	19.7
N	420	420	163

The nQ system

Using the Patients' Personal Device to Assess Neurological Health
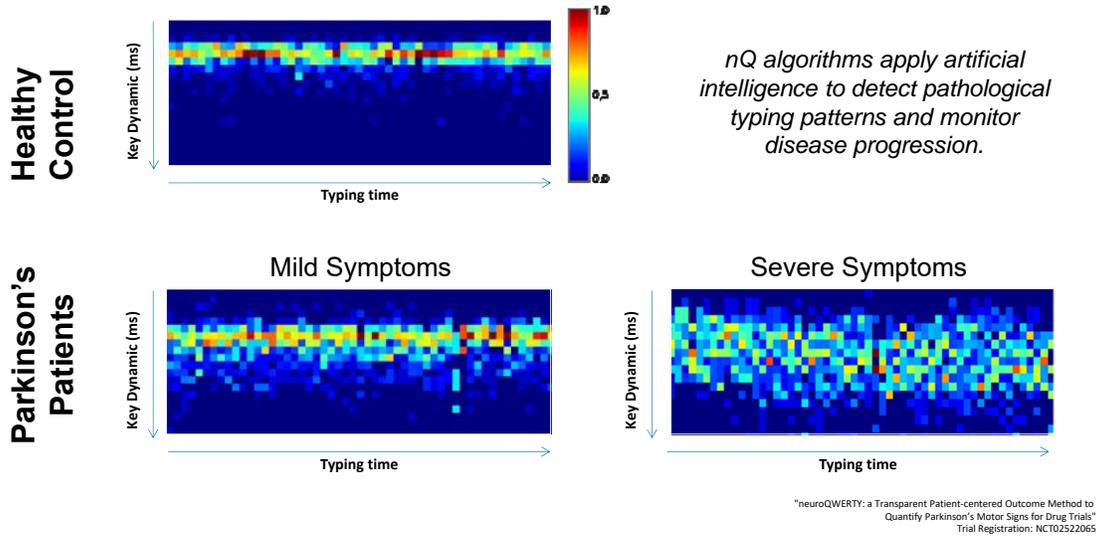
24/7 passive data collection.

No proprietary device. No tasks.

4 Years of Clinical Trials/4 Published Papers validated for
- *Early Detection*
- *Monitoring Disease Progression*
- *Measuring Impact of Therapy*

MIT

Disease Progression Tracking: *What your typing signature reveals*

Healthy Control

Key Dynamic (ms)

Typing time

nQ algorithms apply artificial intelligence to detect pathological typing patterns and monitor disease progression.

Parkinson's Patients

Mild Symptoms

Key Dynamic (ms)

Typing time

Severe Symptoms

Key Dynamic (ms)

Typing time

"neuroQWERTY: a Transparent Patient-centered Outcome Method to Quantify Parkinson's Motor Signs for Drug Trials"
Trial Registration: NCT02522065

Validated, Peer-Reviewed AI Driven Computational Biomarker for Neurodegenerative Disorders

2013

Sleep In
Mechan
N = 14

2014

SCIENTIFIC REPOR

Computer keyboard interaction
an indicator of early Parkinson's
disease

Psychomotor Impairment Detection via
Finger Interactions with a Computer
Keyboard During Natural Typing

zheimer's
oth
= 120
xAD/PD/CNT

Computer keyboard interaction as
early Parkinson's disease

JOURNAL OF MEDICAL INTERNET RESEARCH

Original Paper

Detecting Motor Impairment in Early Parkinson's Disease via
Natural Typing Interaction With Keyboards: Validation of the
neuroQWERTY Approach in an Uncontrolled At-Home Setting

Abstract

Parkinson's D
Mechanical
Patient 0

N = 61
PD=31, CNT=30

>1K Users

ALS
N = 60
30xALS/CNT

Early Detection: 5-10 years sooner than gold standard

"neuroQWERTY: a Transparent Patient-centered Outcome Method to Quantify Parkinson's Motor Signs for Drug Trials"
Trial Registration: NCT02522065

Surviving a pandemic: Clinical Trial Vaccine #2

1 Optimize your study design

2 Make the numbers work for you

3 Recruit, recruit, retain

4 Don't forget the little things
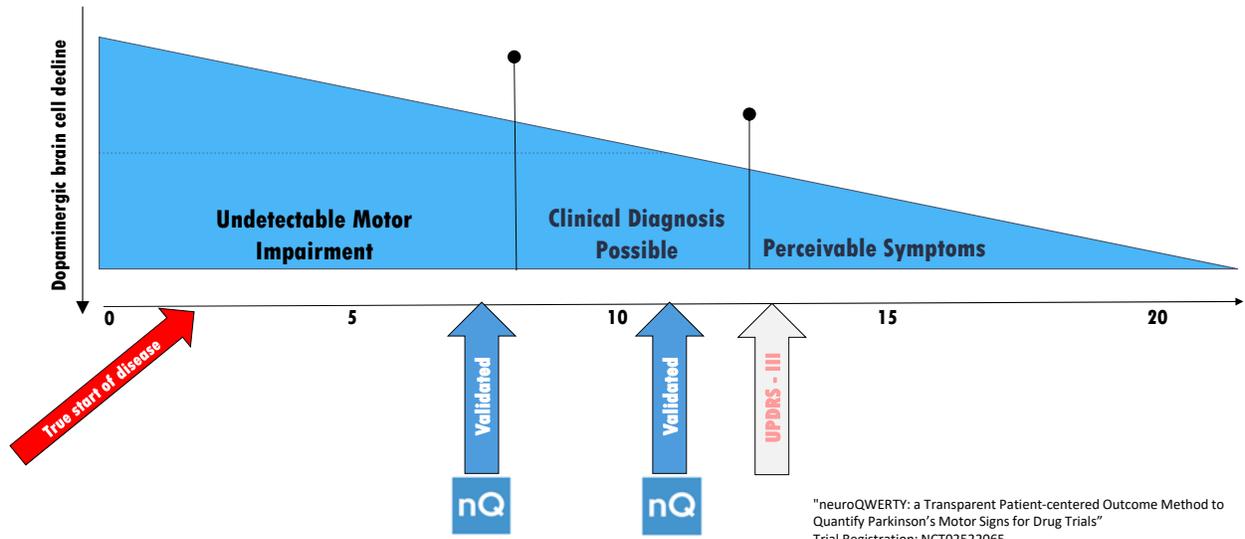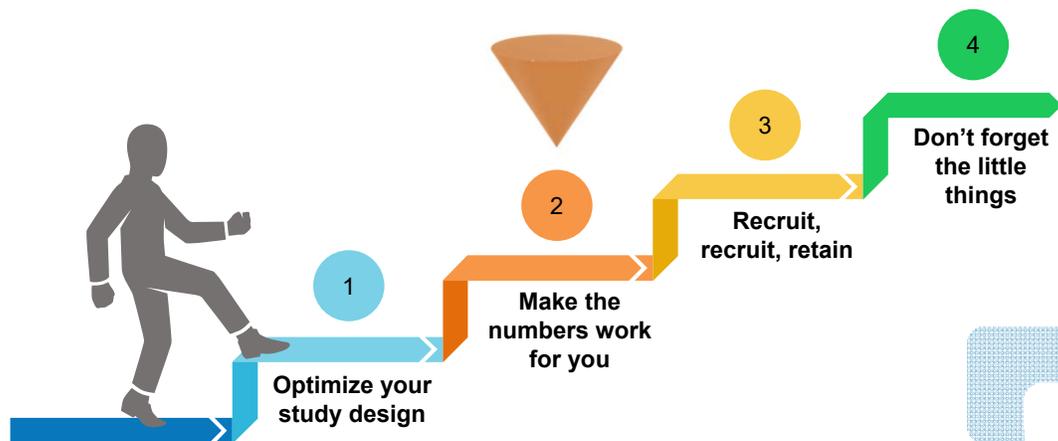
Consider an *Adapative Trial Design* with these challenges

1. Recruitment and related statistical power

2. Efficiency, including financial, administrative and analytical

3. Dosing administrations and safety

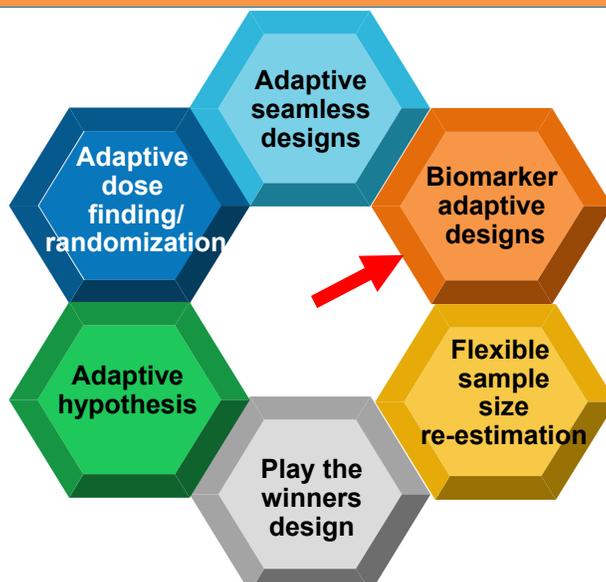4. Difficulty in prospectively defining treatment effects, esp. exploratory studies
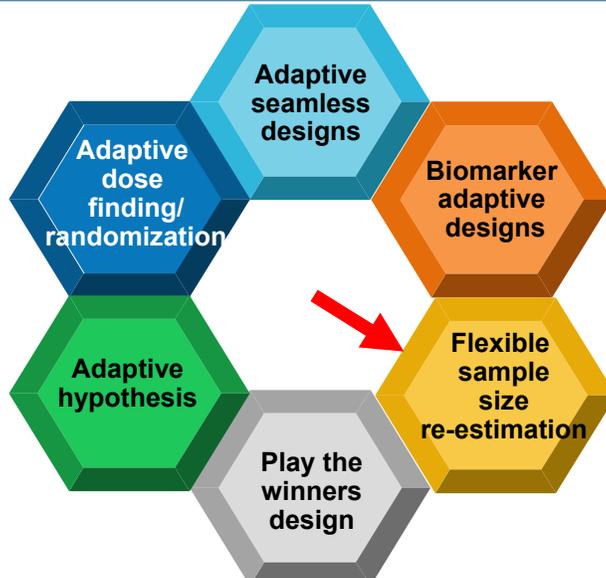
Types of adaptive trial designs
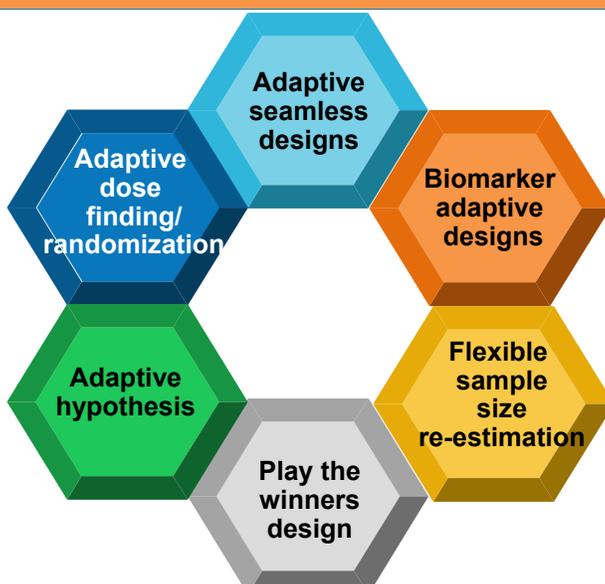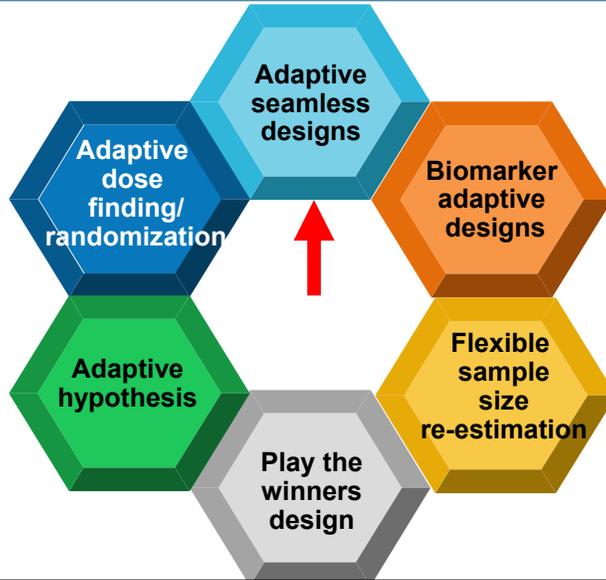
Adaptive seamless designs

Adaptive dose finding/ randomization

Biomarker adaptive designs

Adaptive hypothesis

Play the winners design
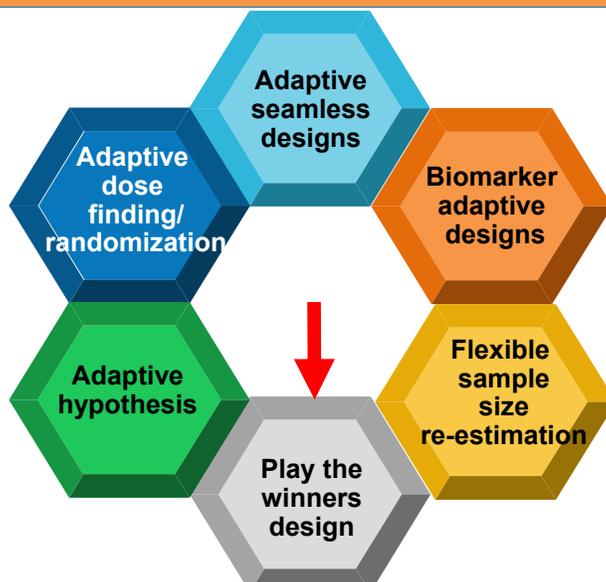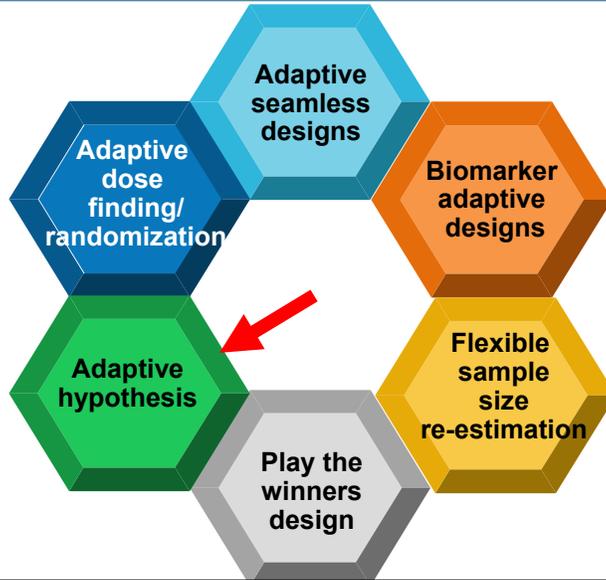
Flexible sample size re-estimation

Types of adaptive trial designs

Types of adaptive trial designs

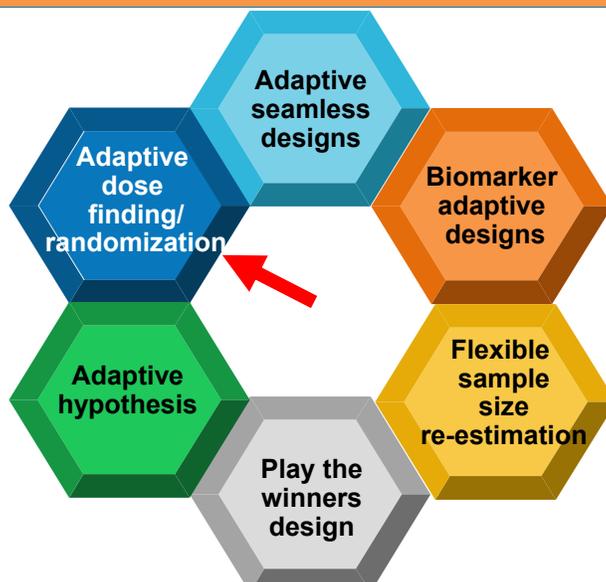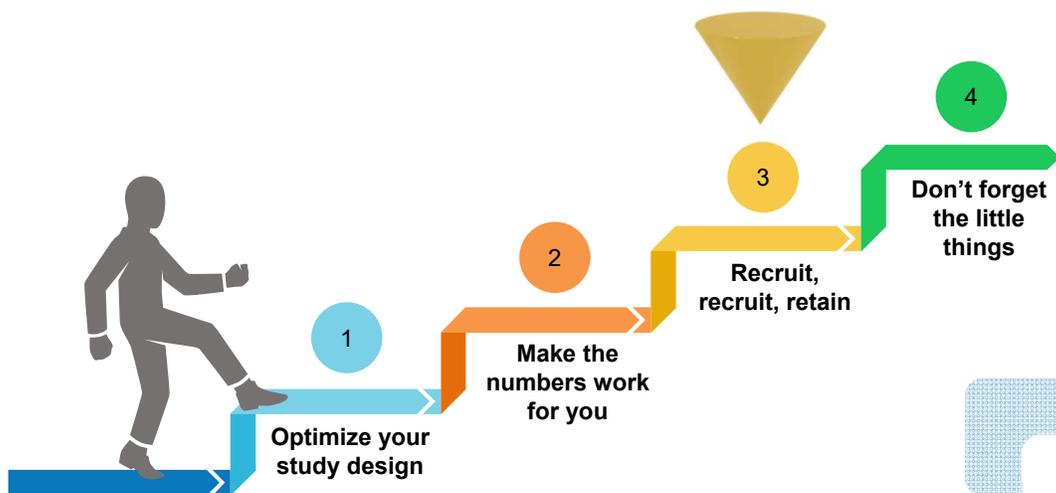# Types of adaptive trial designs

Types of adaptive trial designs

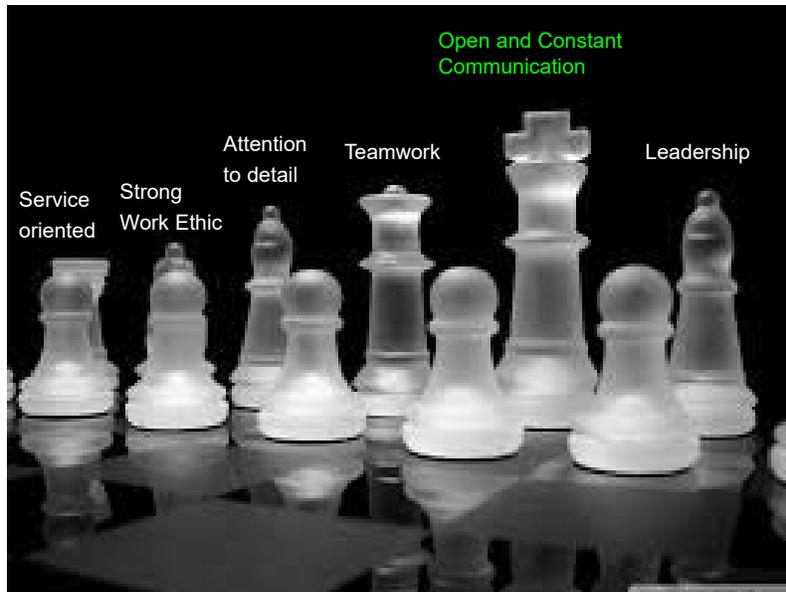# Types of adaptive trial designs

Types of adaptive trial designs

COVID vs outcome measures

Surviving a pandemic: Clinical Trial Vaccine #3

1 — Optimize your study design

2 — Make the numbers work for you

3 — Recruit, recruit, retain

4 — Don't forget the little things

Communication is King

Examples of communication

Keep the list of clinical trials handy

Know how your electronic medical record system can help with recruitment

Recognize the steak

Enrollment and Retention

IRB Compliance

Preparing for monitoring visits

Timely response to querries

Convincing the patient to participate—it's all about the right sequence

1 Overview why the research is important – do not skip this step!

2 Rationale for seeking someone like them

3 Explain the study and answer questions – only after Steps 1 and 2

4 Practice, practice, practice; Do not rush; Show appreciation; Don't forget to follow up
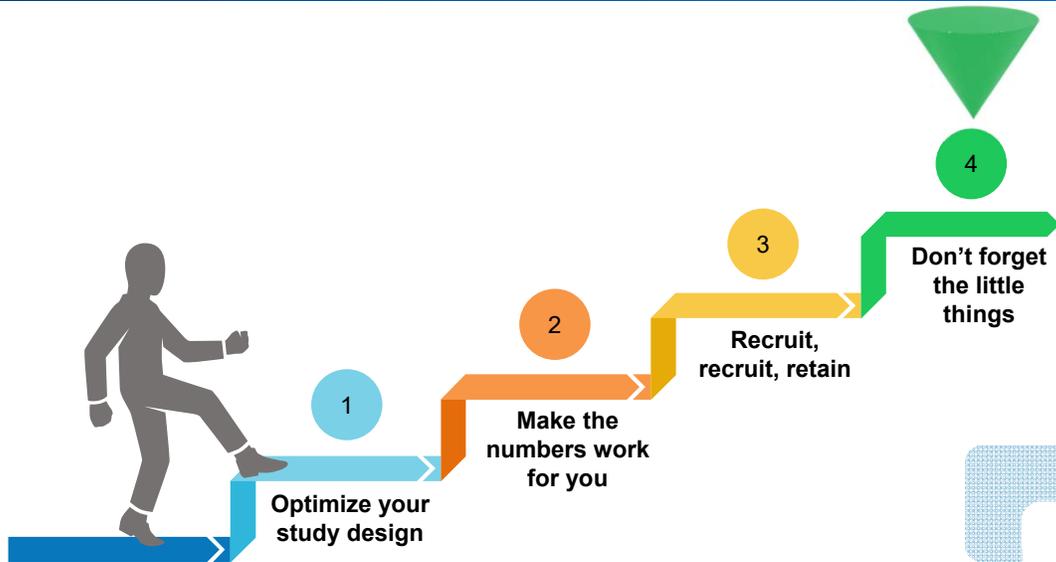
The Michael J. Fox Foundation for Parkinson's Research

Retention strategies

1   Reminder about tests and assessments

2   Study newsletter provided at each in-person visit to inform patient and caregiver about the study

3   Cultivate caregivers throughout the duration of the study through frequent communication about study progress and resources available

4   Share study results back with participants and caregivers

The Michael J. Fox Foundation for Parkinson's Research

Surviving a pandemic: Clinical Trial Vaccine #4

1 Optimize your study design

2 Make the numbers work for you

3 Recruit, recruit, retain

4 Don't forget the little things

All for one and one for all

- Democratic voting process in selecting studies
- Everyone recruits for all studies
- Attention to studies that require help during monthly meetings
- All surplus/residuals go to one bucket
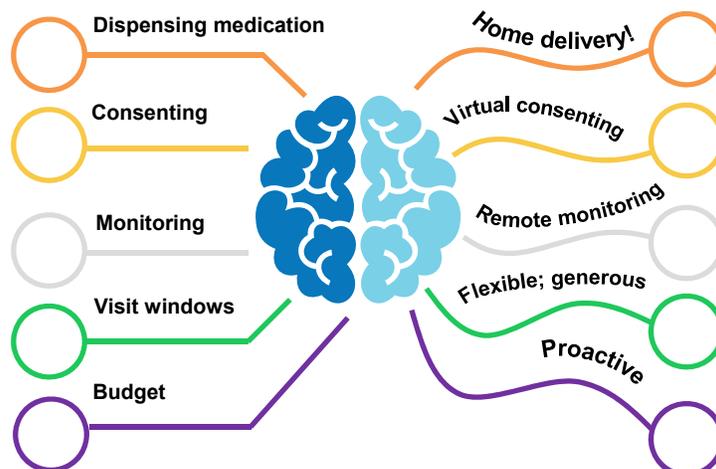
Share the wealth

How can we be better?

- Shortening the contract process: CDA, CTA, Budget Negotiation
- Utilizing EPIC and KP
- Incorporating Regional Neurology, Residents
- Using social media
- Reducing variance in staff participation
- Minority recruitment

OPPORTUNITY AHEAD

Thinking out of the box

Dispensing medication — Home delivery!

Consenting — Virtual consenting

Monitoring — Remote monitoring

Visit windows — Flexible; generous

Budget — Proactive

A few more trade secrets

- The devil is in the details—IRB compliance, budget, documentation, protocol execution
- Hire the best coordinator possible
  - For every 30 minutes you spend with the patient, your coordinator spends 3 hours
- Treat your CROs well
- Show commitment to your sponsors
- Honesty is the best policy