Q: What types of clinical trials do we need to be ready for?

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A: Long term
(progression/disease modification)

&

Short term
(symptomatic treatment effect)

SHORT

A: Long term
(progression/disease modification
& symptomatic treatment)

&

Short term
(symptomatic treatment effect)

Population

Rare
(*n* can be a problem)

Heterogeneity in symptomatology
(posture vs. tremor)

Heterogeneity in areas affected
(focal vs. generalized)

Heterogeneity in etiology
(genetic vs. idiopathic)

CHALLENGE 1

More details in Mark Hallett's talk….

CHALLENGE 2

Regulatory

Do we have the outcome measures that capture what's important to patients and that will lead to FDA approval?

Do we know what clinically meaningful change is for all dystonia? Cervical dystonia? Blepharospasm?

CHALLENGE 3

Timing

In long-term trials, how long is long?

What is progression? How is it defined?

Are there any biomarkers that can be surrogates for progression in dystonia to shorten trial duration in disease-modifying therapy?

In short-term symptomatic therapeutic trials, what is the ideal time for measuring efficacy?

SHORT TERM CHALLENGES

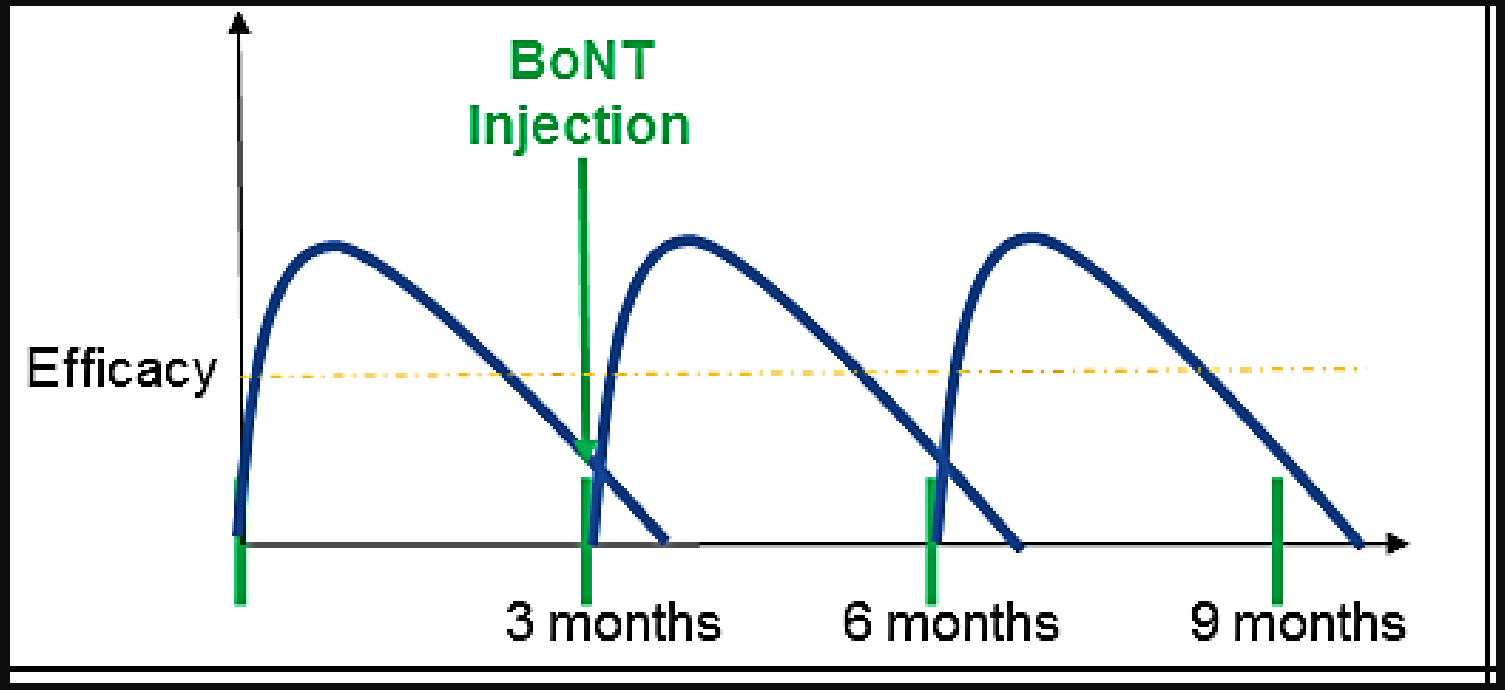
> BoNT is 1st line therapy

> Lifelong condition requiring therapy for decades

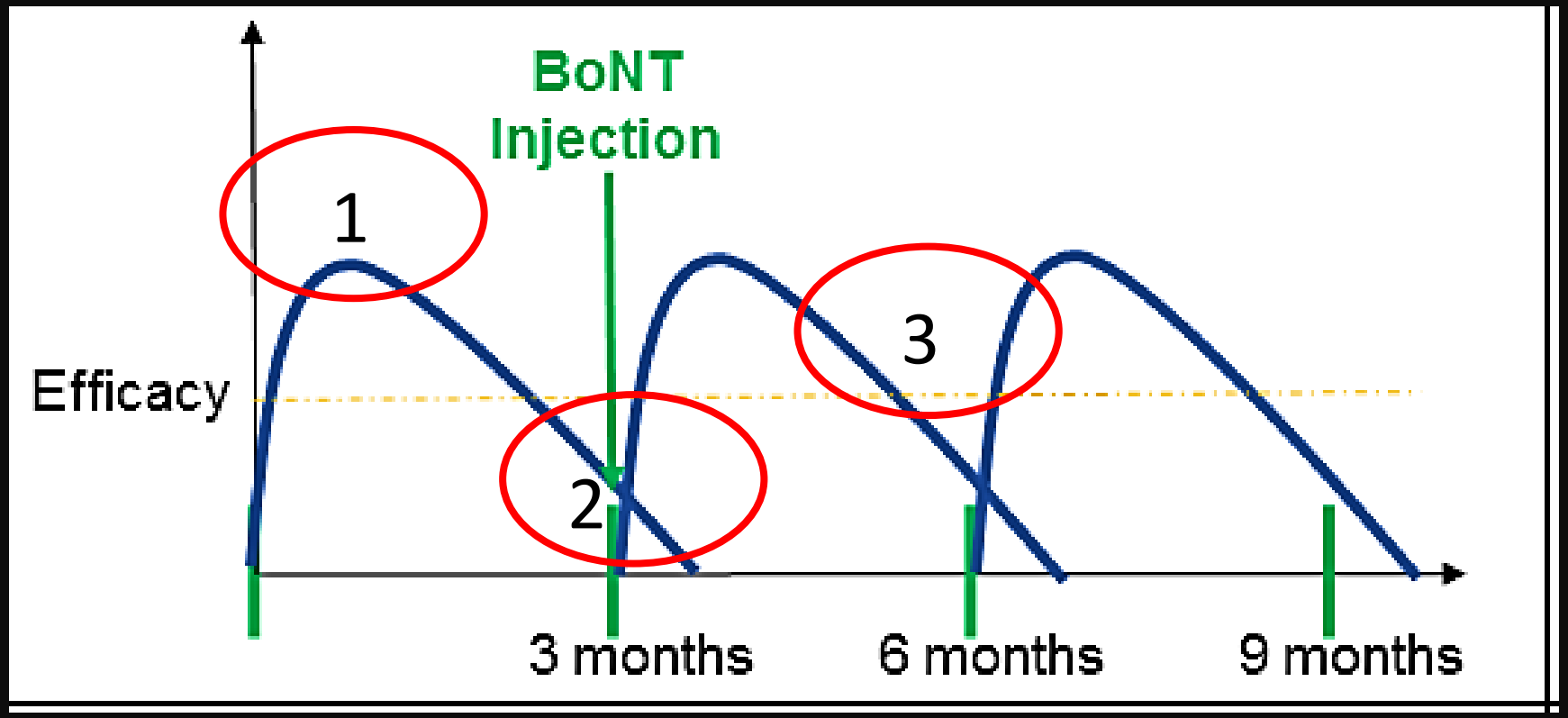
> BoNT improves motor function, QOL and pain

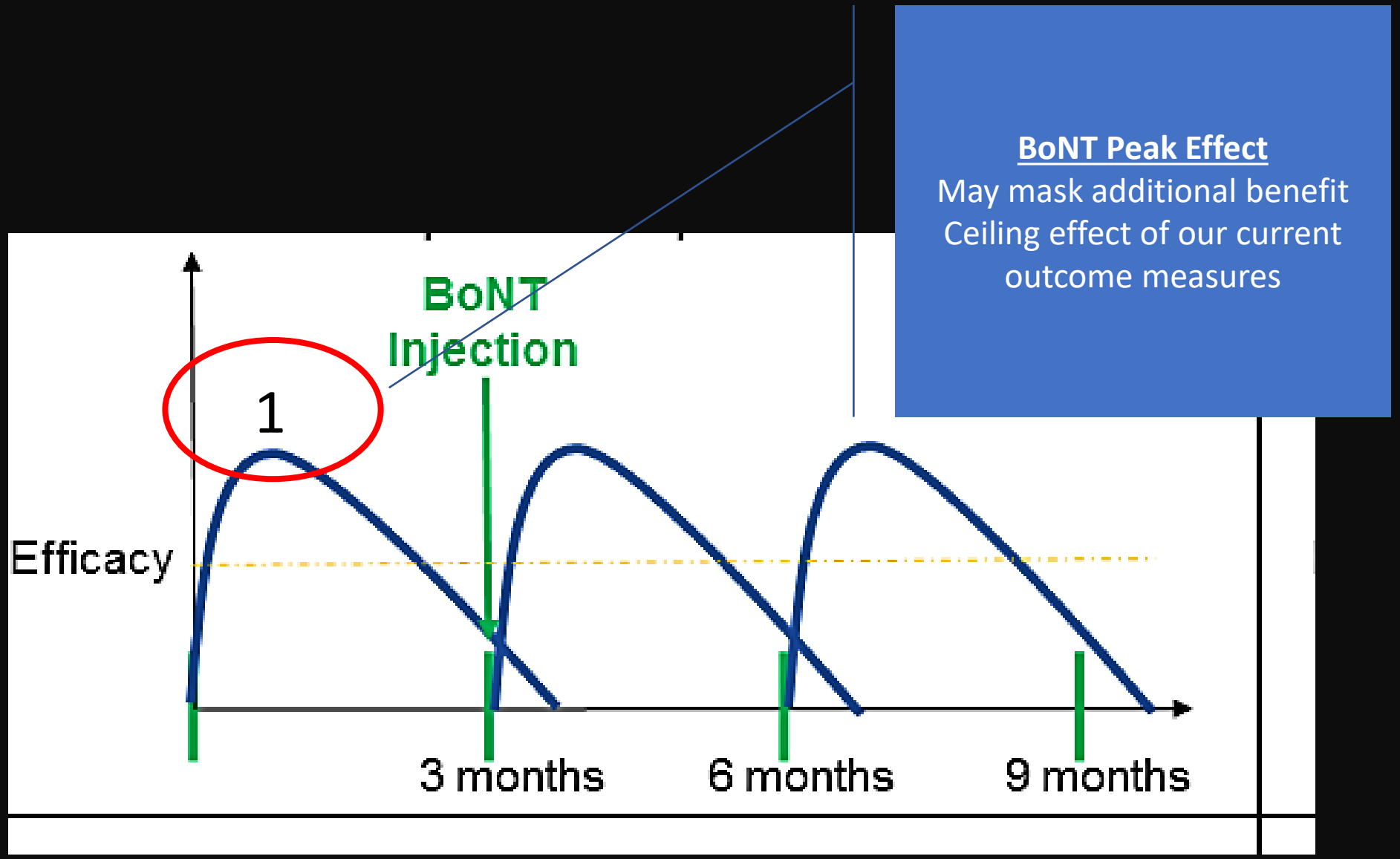
> Improvements may not meet patient expectations

TYPICAL TREATMENT CYCLE



Pirio Richardson & Jinnah. New approaches to discovering drugs that treat dystonias. Expert Opin Drug Discov 2019 Sep


BoNT
Injection
1
2
3
Efficacy
3 months
6 months
9 months



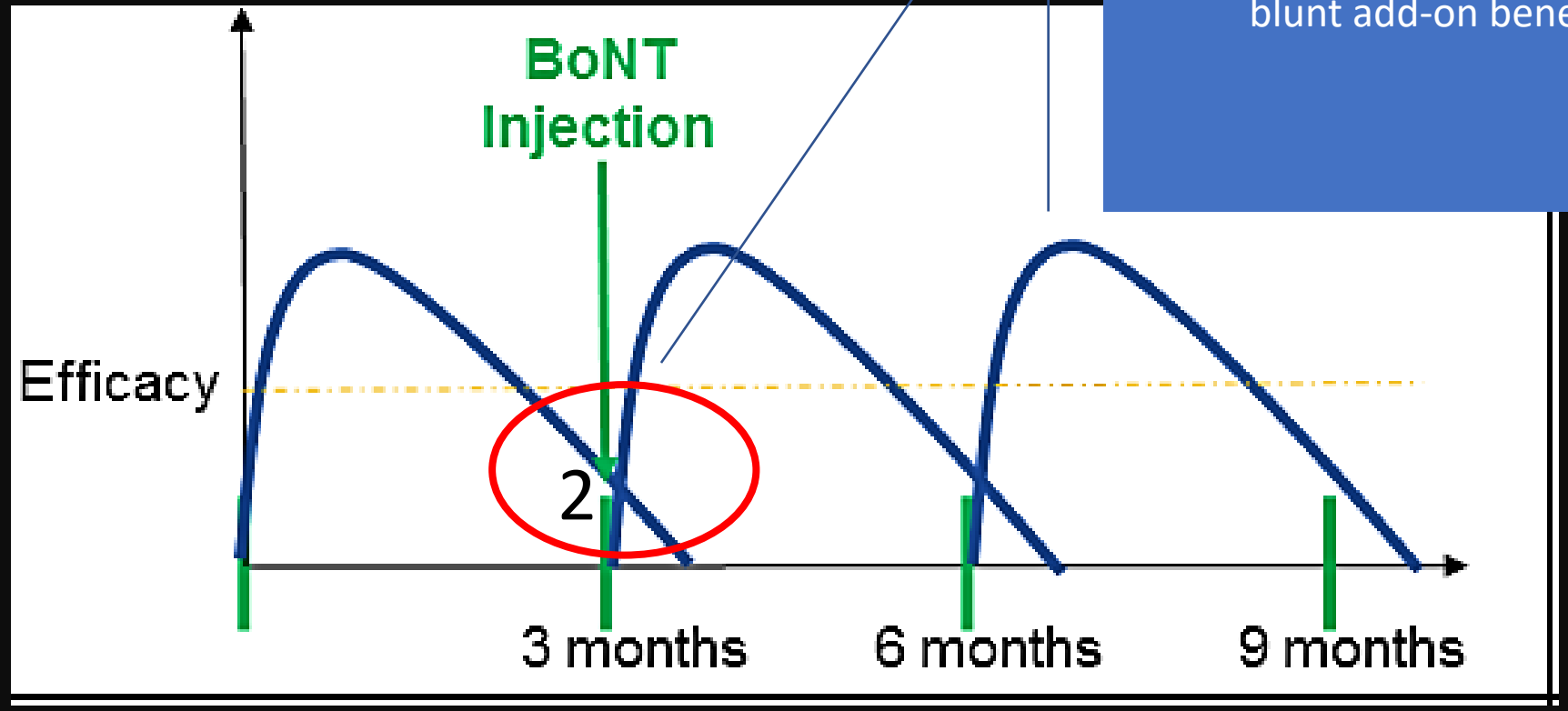
BoNT Peak Effect

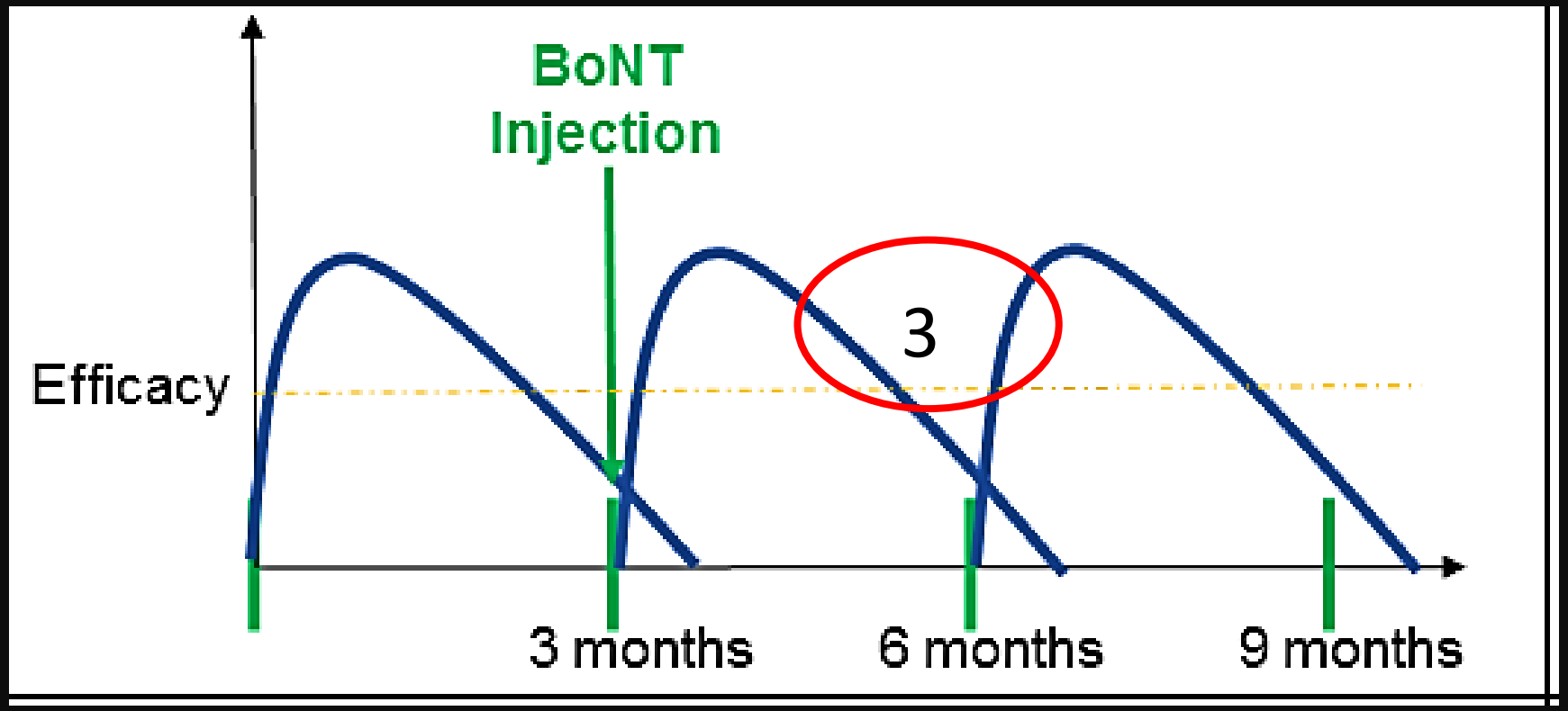
May mask additional benefit

Ceiling effect of our current outcome measures

BoNT Nadir Effect

Negative motor/pain/psychosocial effects at end of BoNT effect may blunt add-on benefit

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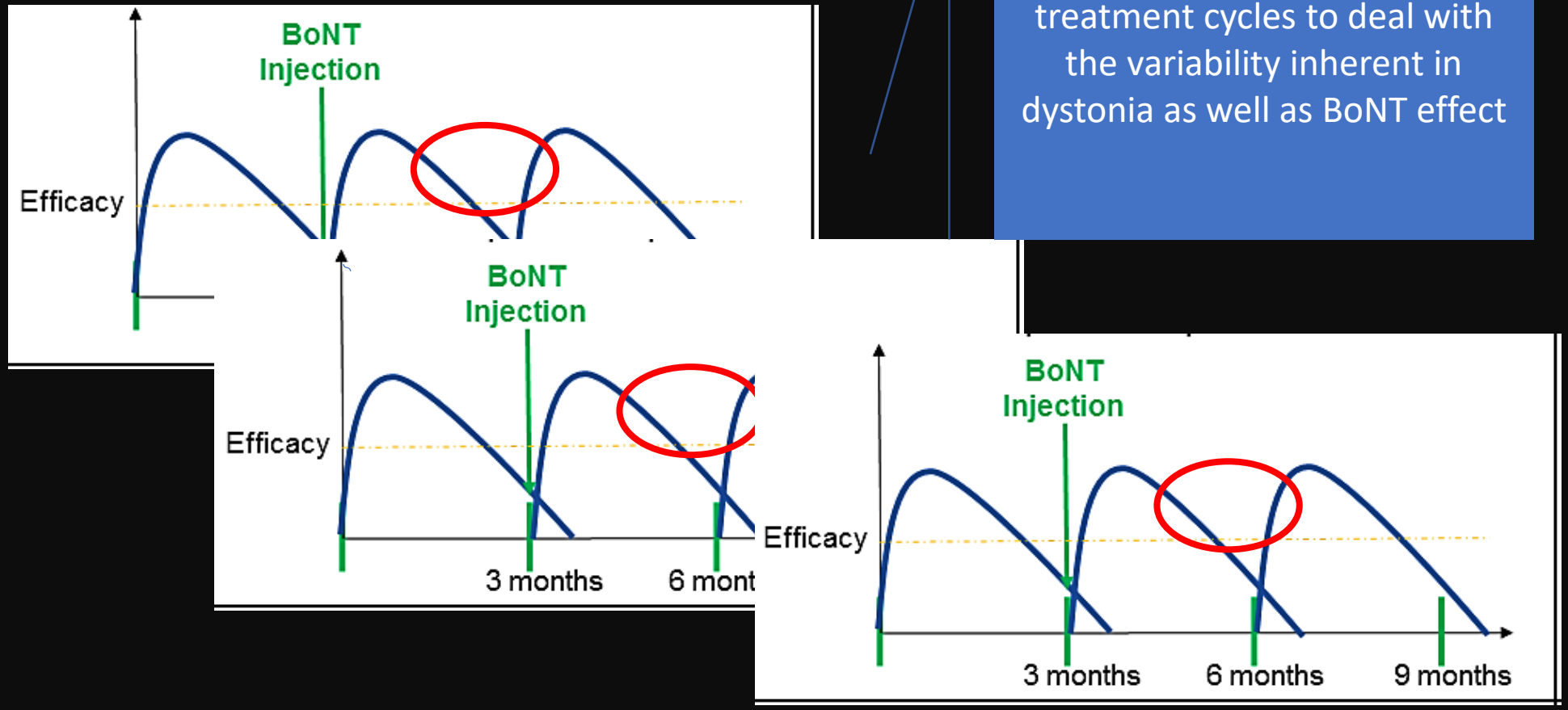


To assess change in baseline with add-on therapy may need to evaluate over many treatment cycles to deal with the variability inherent in dystonia as well as BoNT effect

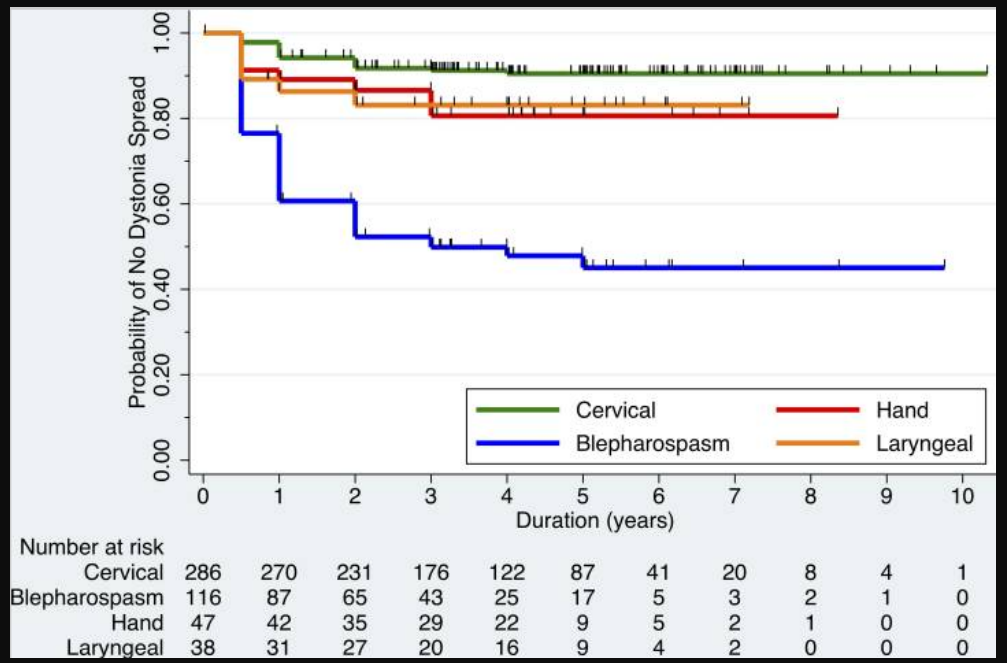
And need “real world” data on this effect (DC Project 2)

LONG TERM SOLUTIONS

Recommendations from IRDiRC Small Population Clinical Trials Task Force

Day, S., Jonker, A.H., Lau, L.P.L. *et al.* Recommendations for the design of small population clinical trials. *Orphanet J Rare Dis* **13,** 195 (2018). https://doi.org/10.1186/s13023-018-0931-2

1. "When feasible, make full use of longitudinal data…"
   - This may allow reduction in sample size
   - "How treatment effect develops?" vs. "What is the effect at a given time?"



Berman et al. JNNP 2020 Mar 91(3): 314-320

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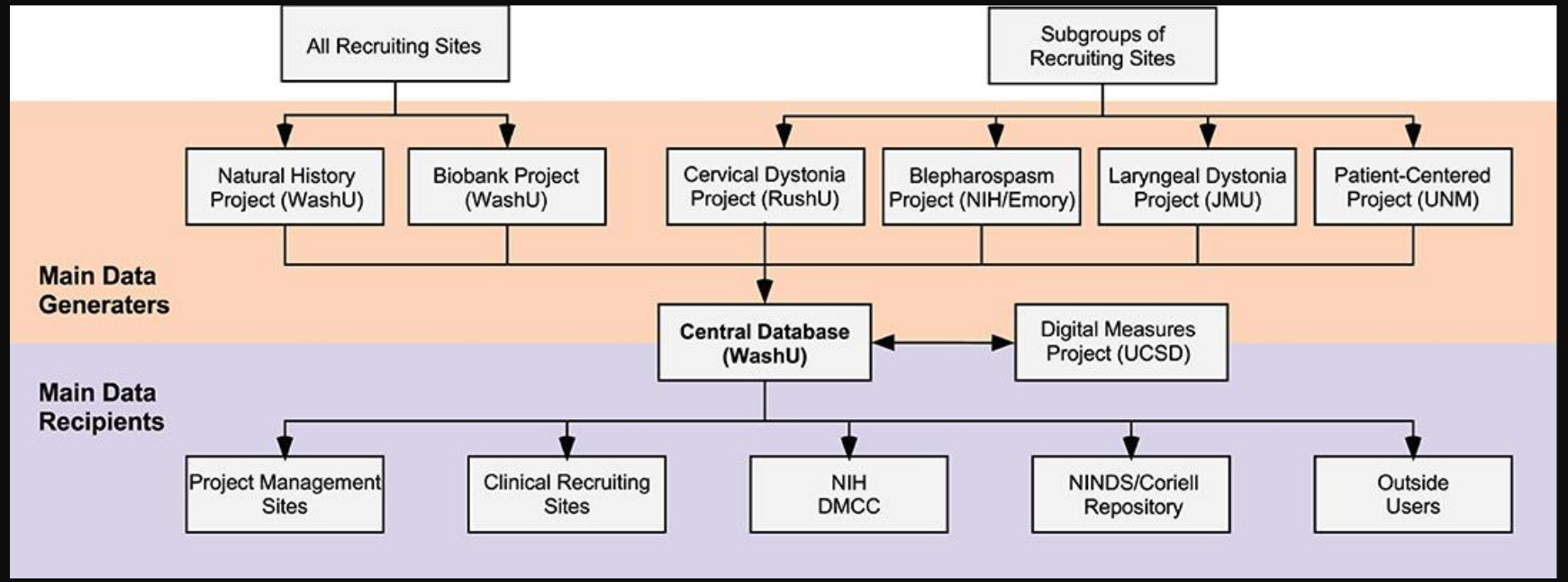
2. "There is an ongoing need for rigorously collected natural history and patient registry data for rare diseases for the design of clinical trials"
   - Also allows for –omic comparison for patients to serve as their own control



Kilic-Berkmen et al. Front. Neurol. 2021 Apr
https://doi.org/10.3389/fneur.2021.660909

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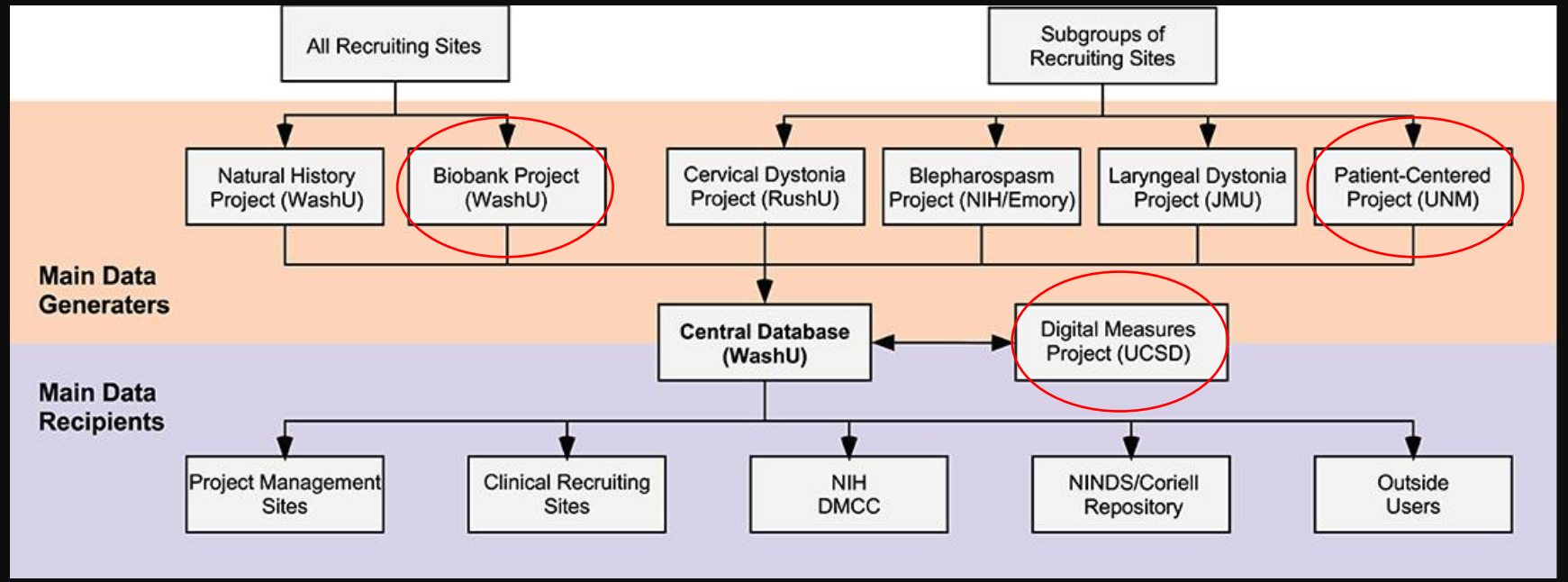
3. "Use multiple endpoints" & "Do not dichotomise continuous endpoints…."
   - "responders" vs. "non-responders" may help with patient enrichment for future trials but if this will require more patients to demonstrate treatment effect



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Conclusions

To overcome significant challenges in designing and conducting adequate and well-controlled rare disease trials, we support ***innovative trial designs and analyses*** provided they are well thought through, justified, and able to

> ***"distinguish the effect of a drug from other influences,*** *such as spontaneous change in the course of the disease, placebo effect, or biased observation."*[1]

[1] *21 CFR 314.126*

Yan Wang PhD "Trial Design and Statistical Considerations in Rare Disease Clinical Trials" Mitochondrial Symposium, Sept 6, 2019. https://www.fda.gov/media/131882/download