nQ-Medical's Immediate Impact on Efficiencies in Clinical Development of Neurologic Therapeutics

Exorbitant Costs and Inefficiencies of Drug Development

The pharmaceutical industry, on average, incurs a cost to bring each new compound through to approval at an estimated cost of $2.8B. For Alzheimer's Disease (AD), as an example, drug development costs substantially exceed other therapeutic areas with total costs of a traditional AD drug development (including cost of capital, cost of failures) estimated at $5.6B often taking over 13 years from preclinical studies to approval by the FDA.[1]

In comparison, estimated cost of a cancer treatment development is $794M (at a 9% cost of capital). Clinical trials represent the most expensive phase of the drug development process.[1]

Table 1
Cost and duration of each aspect of AD drug development

Stage of process	Duration (months)	Cost (billions)* ($)	Cumulative out-of- pocket costs (at end of each stage) (millions) ($)
Preclinical	50.1	1.65	
Phase I	12.8	1.19	71
Phase II	27.7	1.04	126
Phase III	50.9	1.79	413
FDA	18	0.02	
Total	13.3 years	5.69	

Abbreviations: AD, Alzheimer's disease; FDA, Food and Drug Administration.

*Capitalized and including cost of failures of drug development (from Scott et al, 2014) [12].

Phase III trials are the costliest part of AD drug development. *Table 1 from Cummings et al shows the average cost and duration of each phase of AD drug development. These figures include the cost of capital and the cost of failures that companies sustain (3rd column) working in the AD drug development arena. Even out-of-pocket costs for development of a single AD agent approach $500M (4th column).* [1]

Drug developers face significant clinical trial challenges and cost burdens around patient recruitment, retention, and adherence. These increasing complexities and costs of on-site monitoring are further inflamed by increasing payor and regulatory pressure for proof of value.

Forbes recently summarized that about 80% of pharmaceutical trials do not meet enrollment deadlines, resulting in an average loss up to $1.3M per day for a given drug candidate.[2] Additionally, about 37% of research sites fail to meet their enrollment targets, and 10% fail to even recruit a single patient for the study. Based on these industry estimates, a lack of patient-centric trial designs leads to 35% of patients dropping out of clinical trials. Another 35% do not adhere to study protocols, costing about $1M per trial in lost productivity alone.[2]

Drug developers within Neurology space face even greater challenges as probability of success for CNS therapeutic Phase 3 Clinical trials is much lower than other disease areas at 33% (Cardiovascular 74%, Anti-Cancer 62%).[6] Within Neurology, AD Trials have a specifically low rate of success evidenced by exorbitant development costs when failure rates are included (Table 1).[1]

nQ Immediate Efficiency Opportunities - *Patient Segmentation*

Patient segmentation is critical to the success of a drug development and clinical trial program. Taking AD as an example, multiple failures in clinical trials over the past decade are likely due to incorrect patient selection, eg, screening and testing on advanced dementia instead of

early/prodromal disease. It is quite possible that efficacious compounds have likely been shelved after being tested in inappropriate patient segments.

The FDA's *2019 Guidance to Industry on Enrichment Strategies for Clinical Trials* encourages drug developers to identify patient segmentation strategies to 1) decrease variability; 2) increase prognostic enrichment by selection of patients at high risk of disease-related endpoints; 3) increase predictive enrichment by selection of patient subsegments with disease stages more likely to respond to drug treatment. In the words of the FDA, these type of strategies can be expected to power an "*increased number of events in a shorter time period, generally allowing for a smaller sample size…even an imperfectly characterized predictive marker can greatly increase the power and likelihood of study success*." [3]

nQ plays an important role in each of these patient segmentation and enrichment strategies:

- *Decreasing variability:*

    - As the FDA suggests, "*choosing patients with baseline measurements of a disease or a biomarker characterizing the disease in a narrow range*" can decrease variability and increase study power.[3] nQ's ability to give granular quantitation of disease symptoms allows clinical trial designers to define a narrow range of scores for inclusion into the trial to decrease heterogeneity.

    - As the FDA further suggests "*excluding patients whose disease or symptoms improve spontaneously or whose measurements are highly variable*" can decreased intra-patient variability and increase study power[3]. nQ's ability to provide repeated quantitative assessments continuously between clinic visits allows trial designs which include a pre-randomization baseline "run-in" period whereby patients whose symptoms resolve spontaneously or have highly variable baseline symptoms could be excluded. The decreased variability provided by these strategies would increase study power.

    - The FDA adds "*identifying and selecting patients likely to adhere to treatment*" would decrease variability[3]. nQ's ability to detect known drug effect (eg Parkinson's Disease [PD] patients taking levodopa) allows for monitoring of drug compliance and, in the correct trial context, could allow for monitoring of drug compliance and be used to identify patients likely to adhere to treatment.

  Illustrative examples: The concept of increased clinical trial power can encompass both decreased enrollment numbers and shorter duration. Using nQ to decrease variability and increase clinical trial power would allow for designs with shorter duration. Again taking AD as an example, VitalTransformation predicts that reductions only in the patient identification times during recruitment phase by as little as 25%[#] for a net total decrease of duration by only 4.8 months across Phase 1-3 trials of an AD Drug development program would yield clinical R&D savings of $70M in cost of capital savings alone (at 11% cost of capital).[6]

[#] For illustration purposes only

Increased study power can also allow for smaller trials with decreased number of participants. Not specific to AD, but CNS disorders in general, the cost per patient across for phases 1+2+3 is $34,000 + $39,500 + $40,500 respectively = $114,000 total/patient.[7] For a non-AD CNS clinical trial with 200 patients per arm = 400 total patients, reduction in number of patients by as little as 10%[#] could yield savings > $4.5M in a single development program.

- *Increasing prognostic enrichment (identifying high risk patients for endpoints):*

    - Taking AD as an example, accuracy of diagnosis of AD by clinical assessment alone is only around 70-80% meaning 20-30% of patients in a whole generation of prior clinical trials likely did not even have the disease being attempted to treat.[4] Some newer AD clinical trials (such as Biogen's Aducanumab trial) have tried to confirm AD diagnosis by selecting patients with biomarker evidence of abnormal amyloid in the brain. Unfortunately, those biomarkers for amyloid currently consist of invasive lumbar punctures which many patients refuse or expensive PET scans which are difficult to schedule at a limited number of facilities and cost about $4,000 per scan.

  Illustrative examples: if the goal is to recruit 1,000 cognitively normal individuals who are PET or CSF amyloid positive into a Phase 3 clinical trial, and given that around 30% of cognitively normal individuals above age 65 are expected to be amyloid positive, without enrichment at least 3,334 individuals need to be screened. Using nQ metrics, the screening of patients for subtle symptoms of AD could be accomplished to enrich screening for amyloid using PET scans above the background rate of 30%. Even if performance of nQ metric in AD is imperfect (data pending) and the positive predictive value (PPV) of NQ screening was 60%[#], the number of individuals required to be screened on PET/CSF amyloid to reach 1,000 participants would be cut in half. At the estimated cost of $4,000 per PET scan, the amount of money saved from a reduction of initial PET prescreening scans alone for 1,667[#] individuals is > $6.5M.

  The cost saving above reflects only the pure billing cost of PET testing. Not reflected are further savings due to faster recruitment time from having to schedule fewer scans, fewer patients recruited/screened, fewer clinic visits/clinic overhead, and more rapid study closure. The per-patient cost of recruitment/screening into an AD trial can exceed $100,000/patient.[8] If validated, reducing the number of patients screened from 3,334 to 1,667[#] patients yields savings of >$166M.

  80% of clinical trials face delays of >1month and delays can cost up $1.3M per day[2]; If the time savings from nQ deployment lead to reduction in delays by even 15[#] days this could yield savings of $19M.

- *Increasing predictive enrichment (Identifying more responsive patients for treatment):*

    - As the FDA suggests "*An initial screening for response — a biomarker measurement, eg, early clinical response, or full-fledged clinical response — in an open-label pre-randomization period can be used to identify a responder*

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population that would then be randomized in the controlled study …identifying a responder population, eg, a subset of the overall population with a larger than average response to treatment and studying this population in a clinical trial can provide two major advantages: 1) increased study efficiency or feasibility; and 2) an enhanced benefit-risk relationship for patients in the subset compared to the overall population." [3]

nQ's ability to quantify symptoms and to track them longitudinally can be used to identify responders versus non-responders. The ability to execute this type of tracking in PD patients has clearly been demonstrated in our publication Matarazzo et al.[5]

- Identifying responder and non-responder populations can provide other critical advantages to clinical trial design. Leveraging this type of data can produce unique efficiencies across multiple clinical trials. For example, the FDA suggests using patients who failed or were non-responders to one drug as control subjects in a trial for a different agent which works by a different mechanism. They state, "*A population of non-responders to a different drug can be randomized to the new drug or to the drug they did not respond to. The comparison is enriched with respect to the active control comparison because the population is expected to have a poor response to the original drug compared to the test drug*." [3]

Illustrative examples: Identification of responder and non-responder groups can lead to increased study power and expedited screening between trials allowing for briefer trial durations and fewer participant numbers; the advantages of this is already discussed.

In addition, and perhaps more importantly, clinical trials with known responder groups would increase the probability of success which is an extremely sensitive driver of total drug development cost. To see this effect, we can return to AD as an example and consider Table 1; increases in probability of success affect figures in 3rd column (total cost Phase 1+2+3 = 4.02 billion) which adjust for development failures and cost of capital. We can use a simple toy model which includes cost of capital and probability of success to calculate total cost for each Phase. eg for Phase 1:

$$\frac{\left[Phase\ 1 out\ of\ pocket\ cost\ *\ (1 + annual\ cost\ of\ capital)^{duration\ of\ Phase 1+2+3}\right]}{probability\ of\ success\ of\ Phase\ 1}$$

And so on for Phases 2 and 3...

Using data from Table 1 and 11% cost of capital yields probability of success for Phase 1-3 of 13.2%, 10.5%, 25% respectively. The current total cost of Phase 1 + 2 + 3 per Table 1 is $4.02 billion. Very modest theoretical improvements in probability of success values by relative increases of 5%[#] (ie x1.05) to 13.8%, 11.0%, 26.2% predicts total cost of Phase 1 + 2 + 3 = $3.83 billion for a net saving of >$190M.

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nQ Immediate Efficiency Opportunities - *Clinical Trial Outcome*

In addition to patient segmentation, nQ metrics can provide an early outcome measure in clinical trials indicating compound efficacy for informing critical go/no-go decisions. As mentioned above, Phase 3 clinical trials, especially in neurodegenerative conditions, are the most expensive phase of drug development. Correct decisions about terminating a program early after Phase 2 studies or well-informed early futility analysis during Phase 3 trials are critical decisions involving deployment of multiple hundreds of millions of dollars. Failure to collect or correctly interpret data to inform these decisions can have potentially disastrous consequences as in Biogen's recent Aducanumab experience. Inexpensive testing which even partially informs these critical decisions even in one or two cases easily justifies its cost. Within PD, nQ has demonstrated it can clearly identify patients responding to dopamine therapy versus patients who are not responding[5] providing early, continuous measurement of compound efficacy.

In addition to providing useful proof-of-concept data for guidance of internal Go/No Go decisions, continued data collection and clinical experience with nQ metrics could lead to a superior FDA approval endpoint for neurodegenerative diseases. For an approval endpoint/ outcome, FDA usually requires a new drug to show improvement in an established clinical endpoint with decades of experience and direct relevance to mortality, function, or other clinical meaningfulness. Typing represents an inherently meaningful task with direct relevance to patient function. Furthermore, unlike traditional endpoints which can be difficult to assess or accurately quantify due to subjective clinical assessment (such as UPDRS scale for PD), nQ metrics derived from typing data can be more easily measured and better quantified accurately to allow for increased power in detecting drug effects. Continued data collection with larger numbers of patients, demonstrating correlation to traditional outcomes of function will develop nQ metrics into powerful new approval endpoints for FDA submission in neurologic disease.

Illustrative examples: In Biogen's Aducanumab trial, CSF phospho-Tau (p-Tau) from patient lumbar punctures was reported as an additional endpoint. Although the FDA will not approve a medication based on improvement of a surrogate biomarker such as CSF p-Tau, improvement of p-Tau levels in patients after treatment with anti-amyloid antibody such as aducanumab lends powerful support to an argument for disease-modifying efficacy of the drug and can drive internal decision-making as well as support arguments made to FDA. FDA's *2018 Guidance to Industry on Alzheimer's Disease Drug Development* promotes demonstrating improvement in multiple tests to make arguments for efficacy, "*FDA will consider strongly justified arguments that a persuasive effect on sensitive measures of neuropsychological performance may provide adequate support for a marketing approval…..beneficial effects demonstrated across multiple individual tests would increase the persuasiveness of the finding; conversely, a finding on a single test unsupported by consistent findings on other tests would be less persuasive.*"[9] Similar to p-Tau, nQ can play a role as additional endpoint to drive internal decision-making and lend support to FDA submissions.

The out-of-pocket cost of a Phase 3 AD trial can be $287M per Table 1. While no single test will alone drive the decision to discontinue a development program from Phase 2 to Phase 3, a test such as nQ which drives even 15%[#] of the confidence in correctly making that decision provides value of >$43M.

[#] For illustration purposes only

If with enough experience, nQ could be developed into a surrogate outcome for direct FDA approval based on improvements in nQ scores, this would allow for increased power of clinical trials with smaller numbers and shorter durations, the advantages of which have already been discussed.

Mediating TBI Trial Data Collection Barriers

With continued development of nQ TBI digital biomarkers, efficiencies similar to the above discussion (AD and PD) can be expected in a TBI drug development program through improved data collection, patient segmentation, and outcome measurement. The ability to develop improved patient segmentation strategies and outcome measurement strategies for TBI using nQ technology is enabled by unique advantages in data collection and analysis:

- *Accurate baseline:* Players eager to return to play are well known to falsely impair their baseline performance on standard concussion assessments. This makes detection of new impairments after a concussion in game harder to detect and allows players to remain or return to play. By using passive data collection during natural device use, nQ technology can capture an accurate baseline to enable accurate measurement of change.

- *Rapid assessment:* Early assessment of TBI symptoms is important within 12 hours post-injury. An nQ score can be generated in as little as 15 seconds of smartphone typing. This could enable even in-game, sideline assessment of nQ score. While this could be useful in a clinical trial setting, if validated, an accurate sideline assessment of concussion symptoms would represent a valuable and marketable test independent of any drug development program. Alternatively, assessment of concussion symptoms could begin immediately post-game as the player resumes using his/her device.

- *Continuous measurement:* The younger age group population at higher risk for TBI overlaps significantly with population of high smartphone usage. As already discussed, this provides opportunity for remote monitoring of symptoms and response to medication.

- *Rich data set, adherence:* In addition to information derived from keystroke dynamics, nQ data also reflects smartphone usage patterns. This type of phone usage data is studied in correlation to mood (depression, anxiety, PTSD, etc.), circadian rhythms, and can also be used to monitor compliance with “cognitive rest” (abstinence from reading, TV, smartphone usage, etc.) often prescribed after concussion.

Mediating TBI Patient Segmentation/Outcome Measurement Barriers

A smart patient segmentation strategy is critical to success of a trial and when effectively done can increase power of trial design allowing for shorter clinical trial and smaller sample sizes. The ability to assess outcomes accurately and continuously informs critical go/no-go decisions involving hundreds of millions of dollars in the most expensive phases of a drug development program in the form of:

- Pre-screening with nQ to enrich/increase yield of screening with more expensive tests. Similar to arguments provided above about pre-screening for amyloid PET scans, nQ can be used to increase the yield of more expensive testing such as MRI scans or blood

based genetic and cellular markers.

- By detecting subtle symptoms and quantifying them, nQ scores could be used to decrease variability in patient cohorts, confirm that patients included in a trial had concussions, and possibly quantify severity of TBI.

- Longitudinal assessment of symptoms after concussion allows for identification of which patients are improving and can "return to play" versus patients with continued symptoms developing "post-concussion syndrome." Assessment in even longer timeframes could be used to identify Parkinson-like symptoms and cognitive symptoms commonly found in CTE (chronic traumatic encephalopathy), an otherwise difficult to clinically diagnose condition which can develop after repetitive head trauma.

- Longitudinal assessment of symptoms can identify responder versus non-responder groups which allow for efficient clinical trial design and efficiencies across clinical trials as non-responders from one trial may be effective controls in another trial.

Future State Vision/Promise

Ultimately, typing represents a complex reflection of integrated central and peripheral nervous system function encompassing behavioral, cognitive, language, sensory, psychomotor, and neuromuscular domains of function. Continuous, remote, unobtrusive/passive collection of this rich dataset and its appropriate analysis enables not only immediately visible efficiencies in clinical trial design but multiple other advantages in drug development including screening efficiency, generation of real-world-data and evidence, generation of superior endpoints for efficacy:

- Widespread deployment of nQ to patient cohorts can allow for *in-silico* remote screening of patients for desired symptoms or probability of testing positive for other measures. This screening could be done prior to in-clinic visit allowing for efficient use of in-clinic time.

- Social networking sites could be accessed for remote recruiting. Such remote electronic screening strategies can identify patient populations for clinical trials or drug treatment including patients with limited access to healthcare facilities such as rural populations.

- Widespread deployment of nQ data collection would allow for generation of real-world evidence (RWE) in the context of potentially multiple neurologic diseases simultaneously. Analysis of this observational data in context of other patient data such as that obtained from the EHR can generate RWE for new indications of existing medications, access to new patient populations otherwise not included in clinical trials, and/or satisfaction of post-approval requirements.

- Increasing experience with nQ data in multiple neurological diseases is inherently clinically meaningful and can lead to new clinical endpoints that can be used directly as surrogate endpoints for FDA approval in addition to acting as secondary/exploratory endpoints to help detect the early signals of compound efficacy that drive internal Go/No Go decision making.

Conclusion

Analysis of keystroke dynamics data can be viewed as a digital biopsy of complex central and peripheral nervous system function. Harnessing this data by efficient collection and analysis can allow for innovative enriched clinical trial designs with increased power (shorter durations and smaller size), efficiencies across different trials, and inform critical futility or Go/No Go decisions. Widespread deployment could further allow for remote screening, RWE, and novel approval endpoints. The total value provided by deployment of nQ will vary significantly depending upon details of its implementation, method of calculating valuation, and pending data about nQ performance within various disease areas but achievement in the millions of dollars can be reasonably anticipated.

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