Evolution of Digital Therapeutics: Utilizing Clinical Trials, Reverse Translation, and In Silico Methods for Enhanced Product Lifecycle Management in Chronic Disorders with Episodic Manifestations

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SUBMISSION DETAILS

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Methodological Issue Being Addressed Improving trials of chronic disorders with episodic manifestations through reverse translation and in silico clinical trials, leveraging real-time human clinical data.

Introduction Chronic disorders with episodic manifestations (CDEM) are characterized by acute attacks that accent an otherwise chronic condition. CDEM present unique challenges in trial design due to unpredictable recurrence patterns . Traditional trial methods may not account for this subtlety by making assumptions about intervention timing. Drawing inspiration from digital product lifecycle management, we suggest an iterative development to address this difficulty by reverse translational approach with in silico. We analyzed a longitudinal set of 80,000 individuals with migraine disorder. In Silico clinical trials are computational simulations based on real-world parameters to make predictions about trial effectiveness. Analyzing our large dataset, we have established in silico clinical trial model with parameters that account for the temporal and demographic distribution of migraine. This approach will help optimize future intervention timing and clinical trial recruitment, aiding in study design for migraine and other CDEM.

Methods We analyzed data from 80,000 users of an headache diary, certified as a medical device. A validated algorithm based on the ICHD-3 criteria was used to classify single headache attacks as migraine, tension-type headache, or non-migraine and non-TTH.
We performed a Fourier analysis on the records of those who used the diary regularly for 60 days. Our aim was to extract the dominant migraine frequencies. By applying the Fourier transform, we were able to break down the complex migraine episode data into a series of sinusoidal components. This enabled us to identify common patterns and thus dominant frequencies of migraine occurrence in the study population. We sought to gain a deeper understanding of the cyclical nature of migraine events and potentially uncover insights into the predictability of this condition.
We established an in silico trial platform aimed at determining the mechanisms behind optimizing intervention-timing parameters. These trials provide an avenue for stratifying patients based on an individual’s physiology. Importantly, they allow for the optimization of patient-specific parameters. The ultimate goal of this approach is to exploit computational modeling and simulation to improve the precision of digital neuromodulation interventions in migraine.
The remaining step is to populate the in silico trial with virtual patients generated by using assumptions based on the distribution of the data we have analyzed. Results will be available by the time of presentation.

Results The Fourier analysis uncovered a shared dominant frequency at 7-day intervals for both

men and women. Additionally, a distinctive frequency emerges in women at 28-day intervals, characterized by a broader peak, which manifests within about a 3-day window on either side of day 28.
The observed migraine distributions can be modeled by assuming an underlying biological clock that represents the migraine trigger threshold susceptibility-modulating factors (MTTSMF)
The fluctuating MTTSMF provides a subthreshold signal, ie the biological clock cannot initiate an episode without additional noise that represents additional stressors. In other words, we can model migraine as an stochastic resonance phenomenon. We show that we can populate the in silico trial by generating virtual patients based on such a hypothetical subthreshold biorhythms as the hidden state, and by stochastic external stressors.

Conclusion Our analysis of data from 80,000 individuals provides a guide for transforming the design and implementation of clinical trials for CDEM. The optimized intervention timing derived from in silico trial models address key methodological challenges faced by traditional trial design. Although this study focuses on migraine, the approach developed has applicability to diverse CDEM. As such, this approach has the potential to assist with future clinical trial design of digital and traditional interventions, with implications for patient outcomes and trial success.

Co-Authors

* Presenting Author

First Name	Last Name	Affiliation
Markus *	Dahlem *	Click Therapeutics
Brett M.	Colbert	Click Therapeutics
Felix M.	Schneider	Newsenselab GmbH
Shaheen	Lakhan	Click Therapeutics

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Guidelines I have read and understand the Poster Guidelines

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