Digital health technologies- Regulatory perspective

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Decentralized Clinical Trials

- access to patients
- patient convenience
- difficulties with mobility
- rare diseases

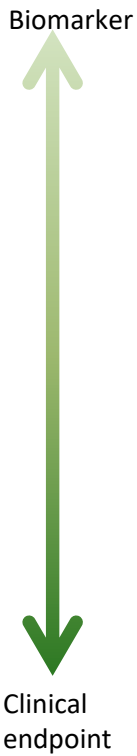
Novel Measurements

- Continuous measurement
- Functionality assessments, accelerometry, GPS, video recording
- Interactive task based tests- vision, hearing , cognition, fine motor coordination
- Physiological measurements
- Photography

Uses of Digital Health Technologies in Clinical Trials

- Endpoints
- Screening and enrichment
- Adherence
- Safety monitoring
- Pharmacodynamics

Summary of endpoints in registrational trials 2007-2015



Type of endpoint	NDAs N=280	Examples of endpoints measured
Chemistry	25%	HBA1c, pregnancy test, GFR
Hematology		Severe neutropenia Apheresis yield > 5 million CD34+ cells/kg
Pathology		Increase/decrease of parabasal cells; biopsy proven acute rejection, clearing of anterior chamber cells
Microbiology		Sustained virological response, plasma viral load, conversion to negative sputum
Imaging +/- (survival, clinical signs)	17%	Bone mineral density; vertebral fractures, spleen volume, progression free survival
Physiological/ functional measurement	9%	6 minute walk, normal sinus rhythm, FEV1, sleep studies
Clinical event /clinical sign	19%	Death, hospitalization, MACE, MS relapse, Lice free head
CRO/PRO	30%	Toronto western spasmodic torticollis rating scale, Hamilton depression rating scale, Rheumatology scale ankylosing spondylitis scale, psoriasis severity index, seizures, sleep, prostate symptom score

Movement and activity (Functionality)

- Sensors
  - Heart failure-6MWD
  - Pulmonary hypertension-6MWD
  - Duchenne's muscular dystrophy 6MWD
- Interactive tests
  - vision, hearing, cognition. coordination

Accelerometry in heart failure

	Lowest Tertile	Middle Tertile	Highest Tertile	*P* Value
ADAU (average daily accelerometry unit)				
NYHA III/IV	59% (19)	44% (15)	36% (12)	0.02
KCCQ physical*	48±26	59±24	65±21	0.002
KCCQ overall*	50±25	58±25	62±21	0.02
MLWHF, physical†	24±11	22±10	21±10	0.08
MLWHFQ, total†	49±24	41±24	43±23	0.16
6MWD, m	242±105	315±112	390±93	<0.0001
NT-proBNP, pg/mL	705±921	485±666	271±262	0.02

Snipelisky et al: Circulation 2017 Volume 10, Issue 6, June 2017

Imaging

- Photographs in dermatology
- Videos of movement disorders

Valbenazine versus placebo for tardive dyskinesia

Table 46: Comparison of 6-week AIMS Baseline and Change Scores Across Controlled Studies

Study*	Treatment Group (N=)	AIMS Baseline mean (SEM)	AIMS CFB mean (SEM)
1201 on-site[1]	Placebo (N=54)	15.3 (0.6)	-2.4 (0.5)
1201 on-site[1]	Valbenazine 50+100 mg pooled (N=53)	14.6 (0.7)	-3.1 (0.6)
1201 post hoc[2]	Placebo (N=46)	8.5 (0.7)	-0.5 (0.4)
1201 post hoc[2]	Valbenazine 50+100 mg pooled (N=40)	7.8 (0.6)	-1.3 (0.5)
1202	Placebo (N=44)	7.9 (0.7)	-1.1 (0.6)
1202	Valbenazine 25-75 mg pooled (N=45)	8.0 (0.5)	-3.6 (0.5)
1304	Placebo (N=76)	9.9 (0.5)	0 (0.4)
1304	Valbenazine 40 mg (N=70)	9.8 (0.5)	-1.8 (0.5)
1304	Valbenazine 80 mg (N=79)	10.4 (0.4)	-3.3 (0.5)

Source: Reviewer-created, using data from Clinical Study Reports for Studies 1201, -1202, and -1304 ITT Analysis Sets

AIMS=AIMS total dyskinesia score (sum of Items 1-7); CFB=change from baseline

*4-digit numbers are prefaced by NBI-98854- for the full study identifier

[1]*On-site rater scores using AIMS score descriptors pre-revision*

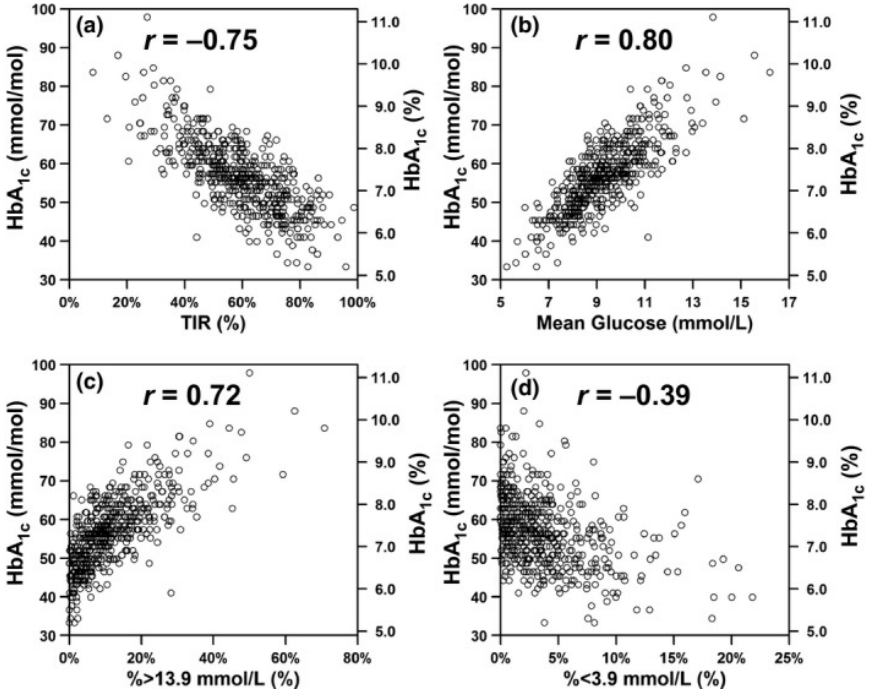
[2]*Post hoc central rater scores using modified AIMS descriptors; Applicant's mITT analysis set excluded subjects without AIMS scores or detectable [+]-α-dihydrotetrabenazine plasma levels at Week 6*

Physiological tests

- ECG for arrhythmia
- Continuous BP monitoring
- EEG for epilepsy
- Pulse oximetry

Biochemical tests

Continuous glucose monitoring versus HBA1C



Hirsch et al. Diabet. Med. 36, 1637–1642 (2019)

- Validation and verification of biosensors
  - Testing that the technology meets its technical specifications
  - Testing that the technology gives precise and accurate results in the study population
  - Comparison with visual or other measures
  - Testing confounders
  - User testing
- Justification of novel endpoints
  - Comparison with existing benchmarks of drug efficacy
  - Consultation with patients, caregivers, disease experts, regulators

Other regulatory considerations

- Suitability for a clinical trial would be determined independent of whether the DHT was cleared by CDRH
- Informed consent
  - Describe expectations of privacy, any physical risks, address expectations of real-time safety monitoring
- Part 11
  - Refers mainly to custody of data, access controls audit trails, preservation of source information