Digital Tools and Remote Monitoring in Drug Development

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Disclaimers & Acknowledgements

Both studies described in publications used as a starting point for this working group were designed and initiated in Q1 and Q2 of 2016, prior to the mobile technologies CTTI recommendations and 2018 Biomarker Qualification Evidentiary Framework FDA Guidance being available publicly

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Chris Benko is Koneksa's CEO and co-founder and a former executive at Merck, he is also an advisor to Takeda Pharmaceuticals. Koneksa's customers are throughout the biopharma industry.

Problem Statement

Clinical trials in normal healthy volunteers (NHV)

The goal of early-stage clinical trials is to establish a pharmacokinetic, pharmacodynamic and safety profile of an investigational drug

- Early stage clinical trials in multiple therapeutic areas, excluding Oncology, are conducted in NHV
  - The PK, PD and safety data are collected while study subjects are confined to the clinical pharmacology units (CPU) and after the discharge from the CPU during the follow-up visits
  - The duration of the confinement varies from one to several weeks depending on the study design, investigational compound properties and anticipated/emerging safety profile
- Safety data collection is done at predefined time points and includes vital signs (e.g. ECG and laboratory safety tests)
- The CPU confinement for extended periods of time is inconvenient for study subjects and may not provide the data reflective of normal day-to-day person's activity
- Little or no safety information
  - Other than subject's memory recall, is available after subject's discharge from the CPU and in-between the follow-up visits making difficult to interpret potential safety findings

COVID-19 related activities

- COVID-19 related symptom monitoring: applications
  - Trials aimed at testing COVID-19 related treatments or vaccines
    - Monitoring vital signs as a proxy for disease incidence prior to confirmation with lab tests
      - Sensor + ePRO
- Moving conventional clinical assessments into a remote mode to protect clinical trial participants
  - PFT, including FEV1
  - Safety monitoring: HR, SpO2, BP

COVID-19 related symptom monitoring: applications

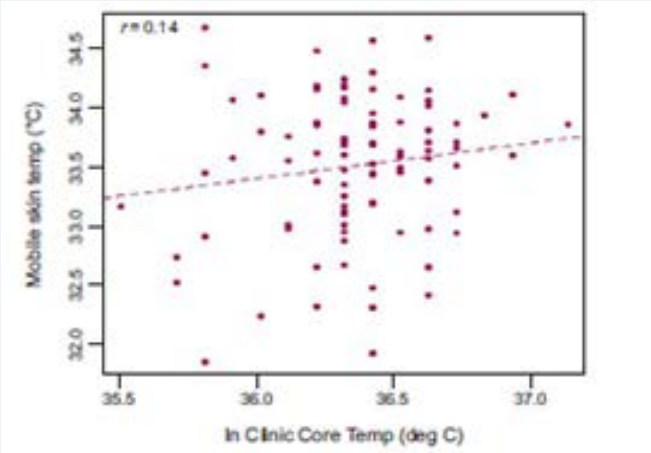
Most recent FDA guidance: https://www.fda.gov/media/136290/download

Device Type	Classification Regulation	Product Code[4]
Clinical electronic thermometer	21 CFR 880.2910	FLL
Electrocardiograph (ECG)	21 CFR 870.2340	DPS
Cardiac monitor	21 CFR 870.2300	DRT, MWI, MSX, PLB
Electrocardiograph software for over-the-counter use	21 CFR 870.2345	QDA
Pulse Oximetry (SpO2)	21 CFR 870.2700	DQA
Non-invasive Blood Pressure (NIBP)	21 CFR 870.1130	DXN
Respiratory Rate/Breathing Frequency	21 CFR 868.2375	BZQ
Electronic Stethoscope	21 CFR 870.1875	DQD

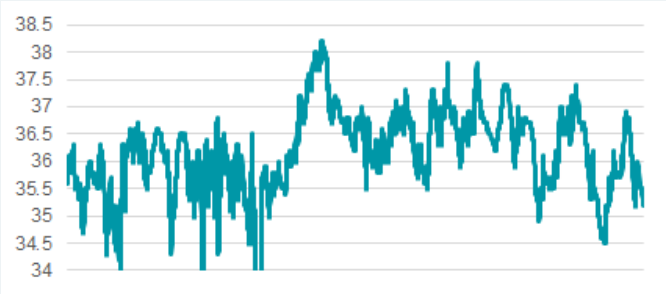
Trials aimed at testing COVID-19 related treatments or vaccines

Monitoring vital signs as a proxy for disease incidence prior to confirmation with lab tests

- Body temperature
  - Regular spot checks with digital thermometers measuring body temperature in the oral cavity
    - Well established reference ranges and reference interval – easier interpretation
  - Continuous auxiliary monitoring
    - Rich data sets
    - More prone to generate aberrant values - more variable data impacted by ambient temperature, clothing and physical activity
    - More difficult to interpret and establish alert thresholds: poor correlation with body temperature measured in body cavities
    - May require normative studies



https://doi.org/10.1111/cts.12602

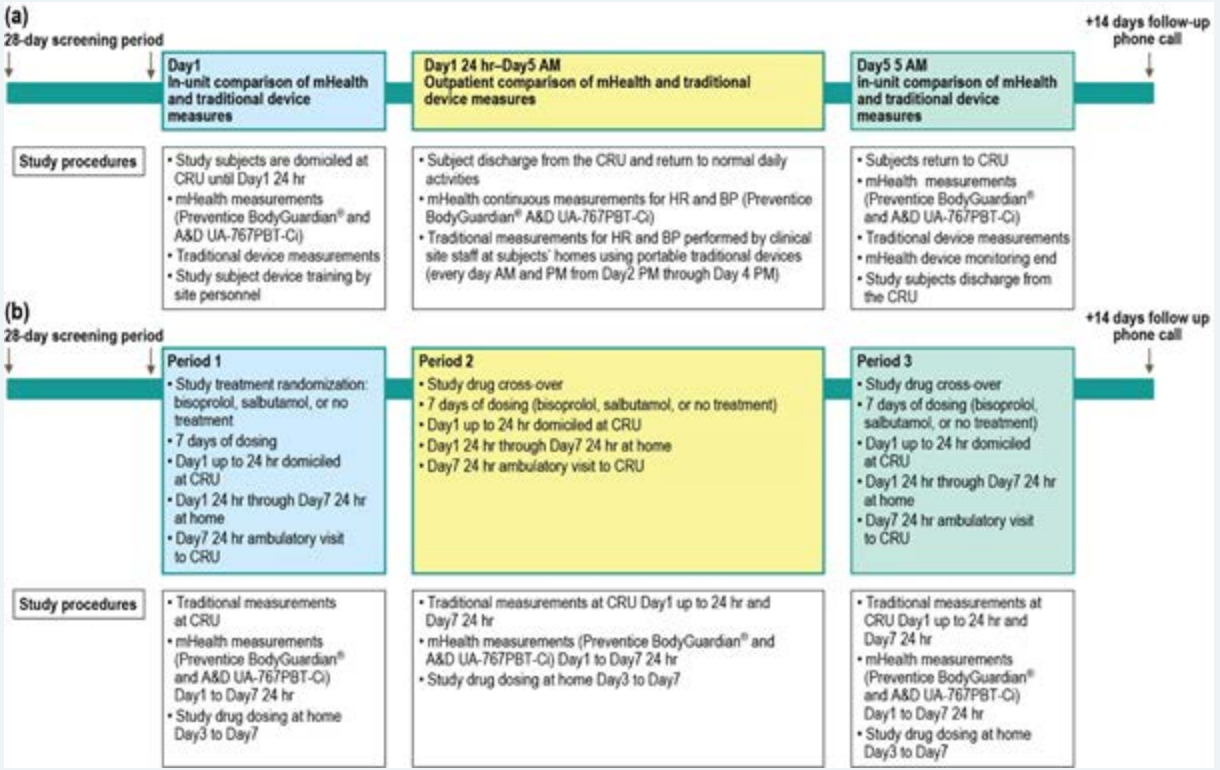


Merck 382 - Validating Mobile Cardiovascular Data

An Open Label, Randomized Clinical Trial to Evaluate Mobile Health Technology for Cardiovascular Monitoring in Healthy Volunteers

Part I

- No intervention
- n = 6 healthy male volunteers
- Goal: Assess the comparability of HR/BP mHealth devices to comparable devices used in the clinic
- mHealth devices: 1-Preventice BodyGuardian Single Lead ECG (HR) 2-A&D UA-767PBT-Ci Blood Pressure Monitor (BP)
- Go/No-Go to Part II: mHealth measurement of HR and BP are sufficiently similar to corresponding measurement by standard method
- **Go criteria achieved**



https://doi.org/10.1002/cpt.1790

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Part II

- Hypothesis: The (reduction/increase) in heart rate at 3 hours postdose on day 3 relative to predose day 1 measured via Preventice BodyGuardian® Heart wearable device is greater in the (Bisoprolol/Salbutamol) group compared to the no treatment group.

		Summary Statistics						Linear Mixed-effects Model			
		N	Day1 Predose	Postdose	Change from Predose	% Change from Predose		Change from Day 1 Predose		Adjusted for Control	
Time	Treatment	n	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		LsMeans (90% CI)	p	LsMeans (90% CI)	p
Day3 3HR	1 Bisoprolol	10	64.4 ± 7.32	63.1 ± 8.56	-1.3 ± 9.55	-1.31 ± 14.56	-0.93 (-7.23, 5.38)	0.79	-11.26 (-17.94, -4.58)	0.01	
	2 Salbutamol	10	67.9 ± 9.36	90.9 ± 11.44	23 ± 10.4	34.89 ± 15.94	22.11 (15.87, 28.35)	<.01	11.77 (5.56, 17.99)	<.01	
	3 Control	11	65.82 ± 6.97	77.09 ± 10.27	11.27 ± 10.39	17.8 ± 16.16	10.34 (5.92, 14.75)	<.01		.	

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