Building Next Generation Clinical Trials

Imaging & Sensor-based technologies

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Digital Medicine & Translational Imaging

Early Clinical Development

Early Clinical Development

Pfizer WORLDWIDE RESEARCH, DEVELOPMENT AND MEDICAL

SCIENCE FOR LIFE-CHANGING IMPACT

Patient Centered Assessments

Clinic

Quantitative

Self

Continuous

Digital Medicine & Translational Imaging

Vision and Impact

Provide end-to-end expertise in the emerging fields of translational imaging, wearable technologies, & continuous monitoring to improve clinical trials and increase the value of medicines for patients

Develop novel digital and imaging endpoints relevant to patients

Quantify Proof of Mechanism & Signs of Clinical Activity

Map path to label for digital data with Regulatory Agencies

Collaborate across the enterprise

Outline of today's talk

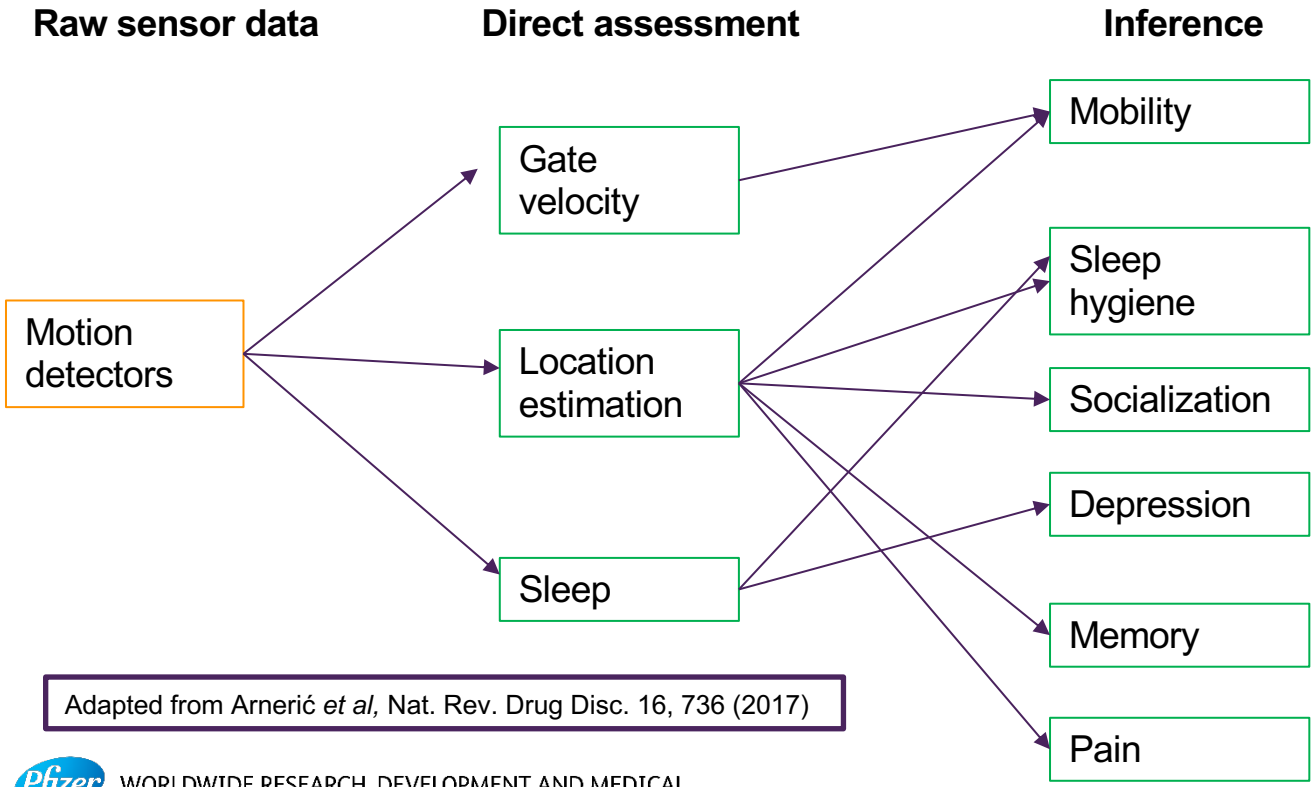
- Some definitions
- Examples
  - Atopic Dermatitis
  - Duchenne Muscular Dystrophy
- Regulatory considerations
- Our laboratory set-up in Cambridge

Different types of digital technologies in clinical research

Digital Technology	Goal
Electronic platforms for recruiting, retention, and data collection	Improve trial management
EDC, eSource, ePRO	Improve quality of data
Digital endpoints	Improve assessment of treatment effect or treatment response
Digital therapeutics	Improve treatment

Adapted from Sverdlov, *et al*, Clin. Pharm. Ther. **104,** 72-80 (2018)

What do we mean by Digital Endpoints?



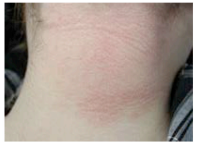
Clinical Outcome Assessment

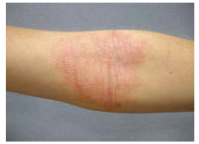
Concept of Interest

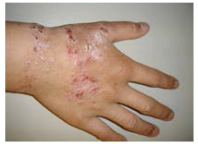
Context of Use

Adapted from Arnerić *et al,* Nat. Rev. Drug Disc. 16, 736 (2017)

Atopic dermatitis (AD) – *the itch that rashes*



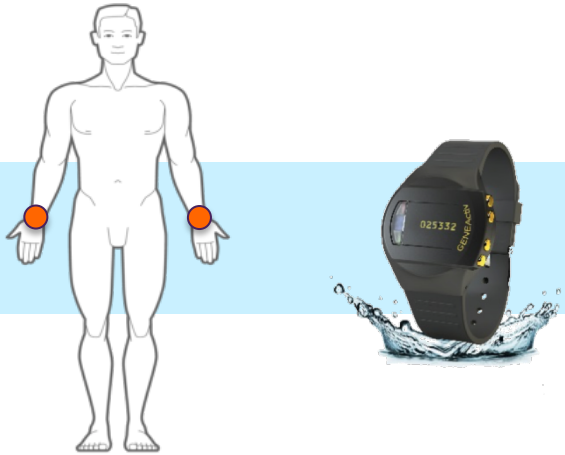


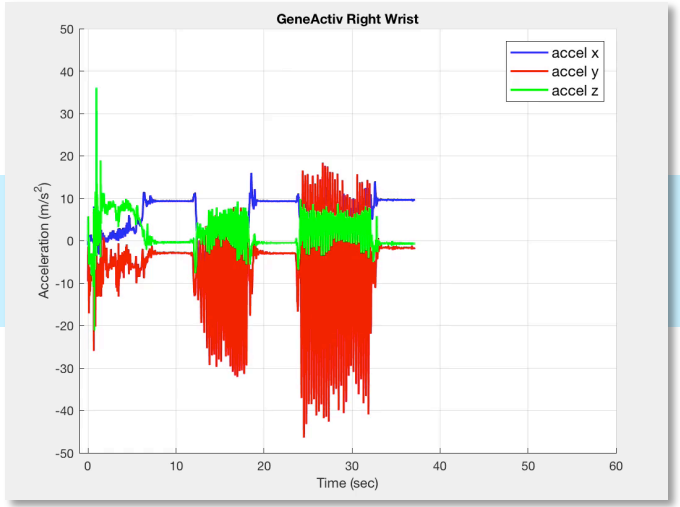


- **Symptoms:** severe itch and sleep disruption (significant issue for patients at night)
- **Current endpoints:** Patient Reported Outcomes (questionnaire)

Goal: Develop objective sensor-based technique to quantify scratch and sleep disruption

How can we quantify scratch / sleep disruption?

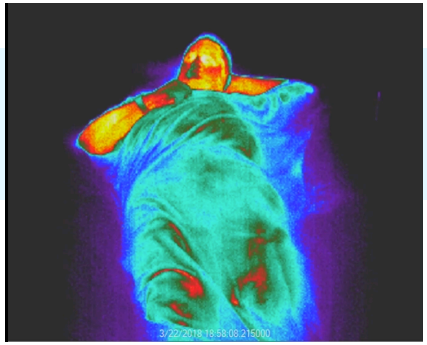




Moreau et al, IEE J Biomed Health Informatics, **22**, 1011-1018 (2017)

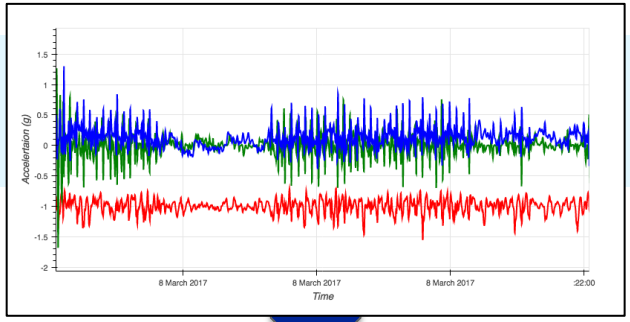
How do we identify a scratching episode?

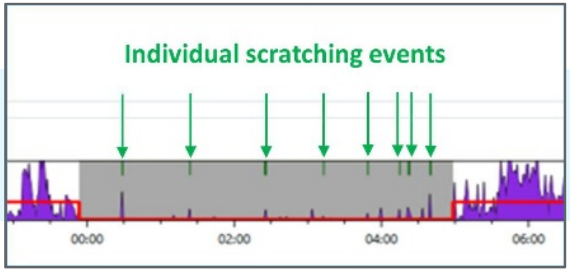
Clinical Phenomenon
(e.g. itchy skin)



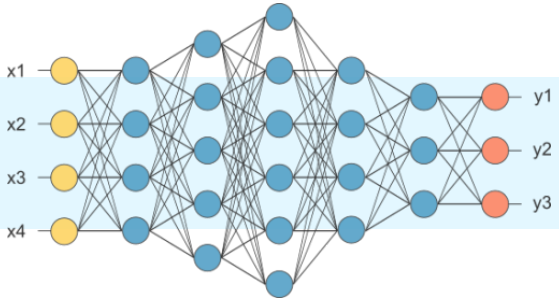
Raw data

Data Transformation
(e.g. feature extraction, annotation)





Measurements

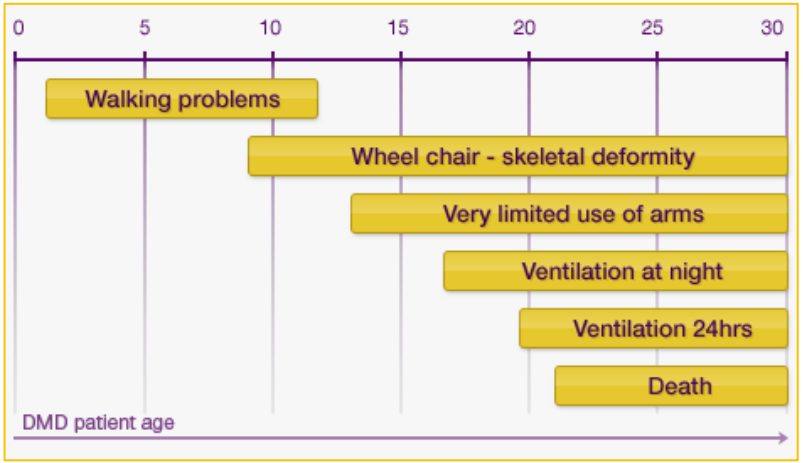


Digital Endpoint
(e.g. scratching & sleep)

Predictive Analytics
(e.g. neural network)

Moreau et al, IEE J Biomed Health Informatics, **22**, 1011-1018 (2017)

Duchenne Muscular Dystrophy (DMD)
– need for new biomarkers and clinical endpoints



- Progressive muscle disease, fatty infiltration, **loss of ambulation**, respiratory and cardiac complications
- Current endpoints: Four-step climb and six-minute walk distance

Challenges of Clinical Functional Assessments for DMD

- Patient compliance
- Single time point
- Maturing population
- Day-to-day variability

- Less focus on quality of movement
- Slow to demonstrate benefit
- May not predict loss of ambulation
- Sensitivity to change is poor

Can wearables capture provide objective assessments of activity in a continuous fashion?

- Continuous measures represent real patient performance during daily life
- Possibility of averaging the data over a period of time (e.g.1 month)
- Reduce dependency of short term clinically meaningless variations that may strongly affect a time-specific assessment.

ActiMyo device – developed by Institute of Myology & Sysnav

Contains	Triaxial accelerometer	Gyroscope	Magnetometer	Barometer
Records	Linear acceleration	Angular velocity	Magnetic field in all directions	Elevation
Enables	Stride length	Stride speed	Distance covered	Number of falls

Use device to calculate: Stride Velocity 95th Centile (SV95C)

- SV95C: measuring top velocity, but is not dependent upon motivation as the 6MWT
- *Loss of top velocity is something patients are very aware of*

www.institut-myologie.org

Steps to qualify the ActiMyo

Validity of gait measurements	• Demonstrate distance measured by device corresponds to ground truth measured manually
Reliability of measurement	• Assess all gait variables • Influence of poor compliance to identify recommended minimal use
Cross validation	• 6MWT (Six Minute Walk Test) • NSAA (North Star Ambulation Assessment)
Sensitivity to change	• Over 6 months and 1 year • Patients over 7 years old walking less than 450m in 6MWT

https://www.ema.europa.eu/documents/

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2018
EMA/CHMP/SAWP/527447/2018
Product Development Scientific Support Department

Draft qualification opinion on stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device*

https://www.ema.europa.eu/documents/regulatory-procedural-guideline/draft-qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular_en.pdf

Draft Context of Use adopted by CHMP

Context of use: Ambulant DMD patients 5 years of age and above.

SV95C measured at ankle is an acceptable secondary endpoint in pivotal or exploratory drug therapeutic studies for regulatory purposes when measured by:

- suitable wearable device* | directly in continuous manner | in home environment

SV95C may also be used to quantify patient's baseline performance in such studies

However, for use as primary endpoint:

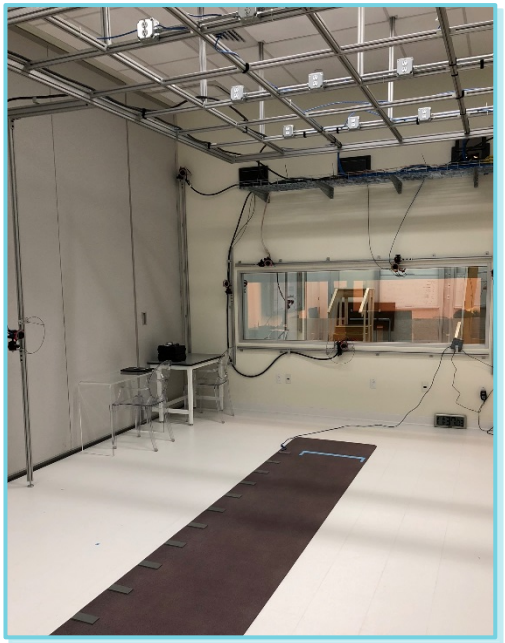
- More robust data gained with additional patients and longer follow-up could be beneficial
- Strengthening the long term correlation to SV95C with functional tests

*Definition of suitable wearable device from CHMP

Device	• Technical requirements • Placement location on body (ankle worn) • Capabilities: stride detection (slow to fast); segmentation of stride; stride length and velocity
Software	• Tests of security • Software development standards • Secure communication
GCP	• Assurance of GCP standards • Complete audit trail from device to the clinical trial database must be established • Patient privacy must be protected
Data & analytics	• Where data stored • Transfer to internet – dedicated secure site • Computation of variables- recording does not rely on individual calibration
Context	• Ability to be used continuously, including home environment

https://www.ema.europa.eu/documents/regulatory-procedural-guideline/draft-qualification-opinion-stride-velocity-95th-centile-secondary-endpoint-duchenne-muscular_en.pdf

Pfizer Innovation Research Lab, Cambridge, MA



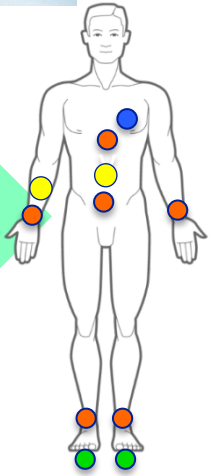
- Compliant instrumented laboratory environment
- Ability to recruit participants for non-interventional studies
- Designed to test novel sensors
- Compare to ground truth measurements
- Major help from many stakeholders across Pfizer

STRYDE Study: *Sensors To Record Your Daily Exercise*

Pf(IR)e Lab

In Clinic Data

4-m walk
Stair climbing
Sit-to-stand
Balance
Grip strength



Devices

GENEActiv
Accelerometer

MC10 Biostamp
ECG

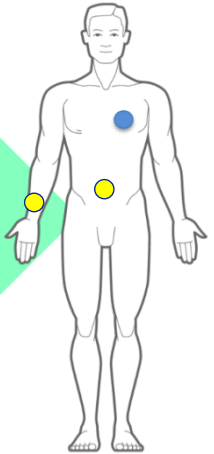
APDM Opals
Accelerometer
Gyroscope

Moticon Insoles
Pressure

18-40 years
65-85 years

At Home Data

Walking periods
Gait quality
Active periods
Sedentary activity
Sleep



Link to external trial in disease population of interest.

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Early Clinical Development

Acknowledgements - *thank you*

Digital Medicine & Translational Imaging colleagues
Our collaborators and volunteers

Thank you for your attention!