Ground Rules

- Tell us how you really feel

- No one will be upset about what you say

- Ask questions

- Hearing your questions is important to us even if we don't have the answer

- You may stop participating at anytime, just let the table leader know

- We will use your feedback to help us decide in what clinical trial situations continuous data collection would be acceptable and what collection devices are preferred.

Lilly

Changing Clinical Development with **Continuomics**

iCAN 2019

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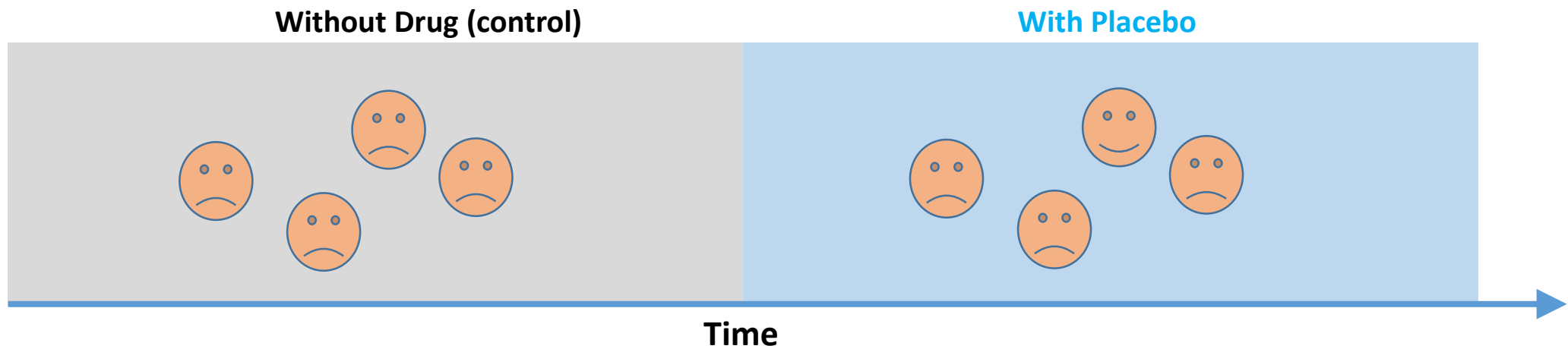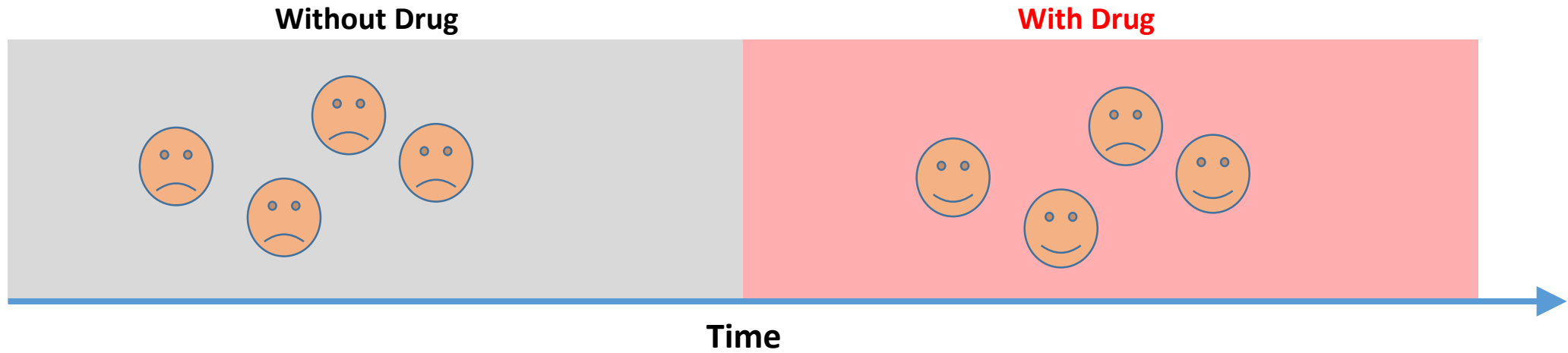Salary and travel support comes from Eli Lilly and Company.
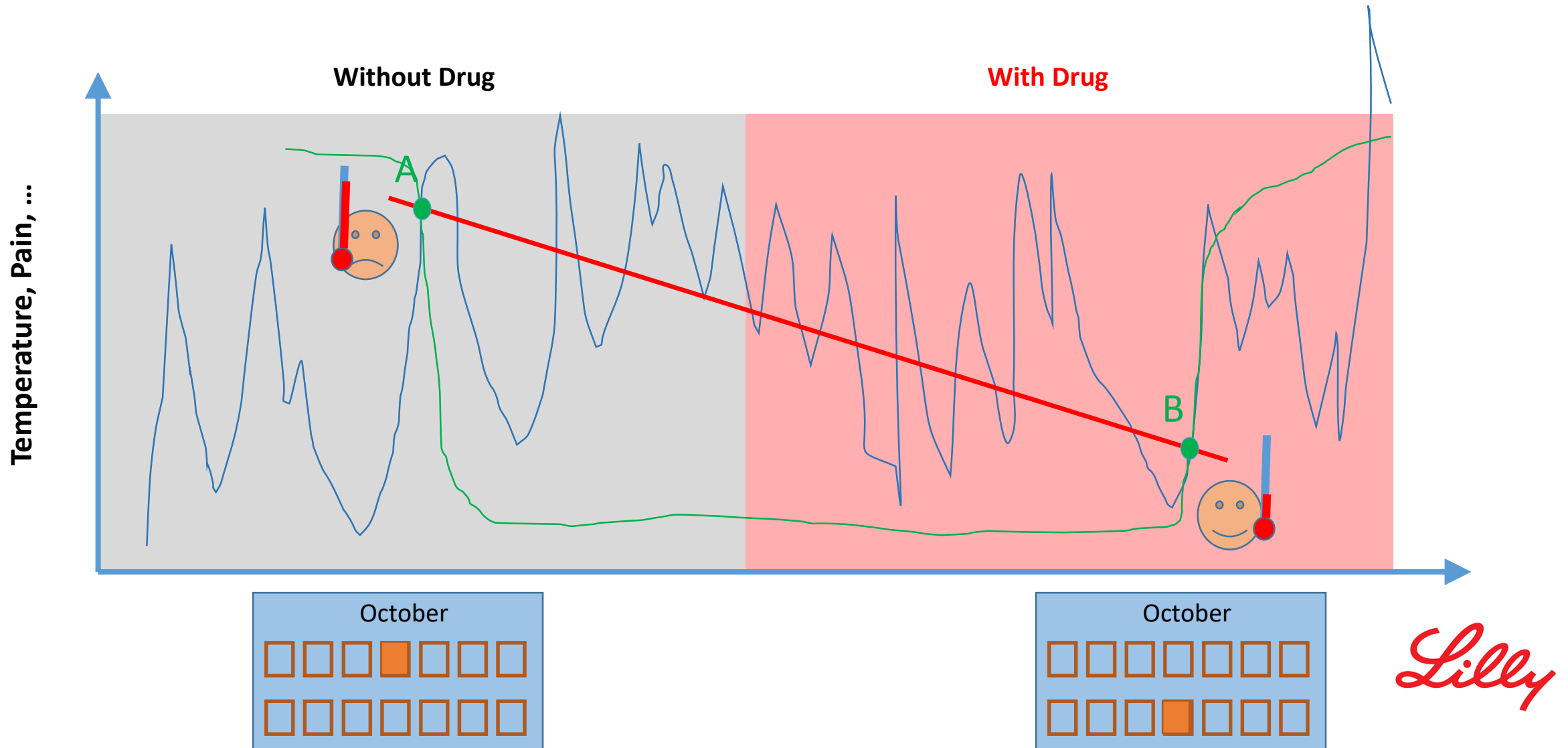
Lilly

We need your help!

What we'll do today:

1) Brief presentation: why measure continuously?
   (10 min)

2) Worksheet
   (5 min)

3) Roundtable discussions
   (40 min)

4) Create a Poster on Level of Comfort with Continuous Data Collection

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Why do we run clinical trials?

How do we measure health in clinical trials?
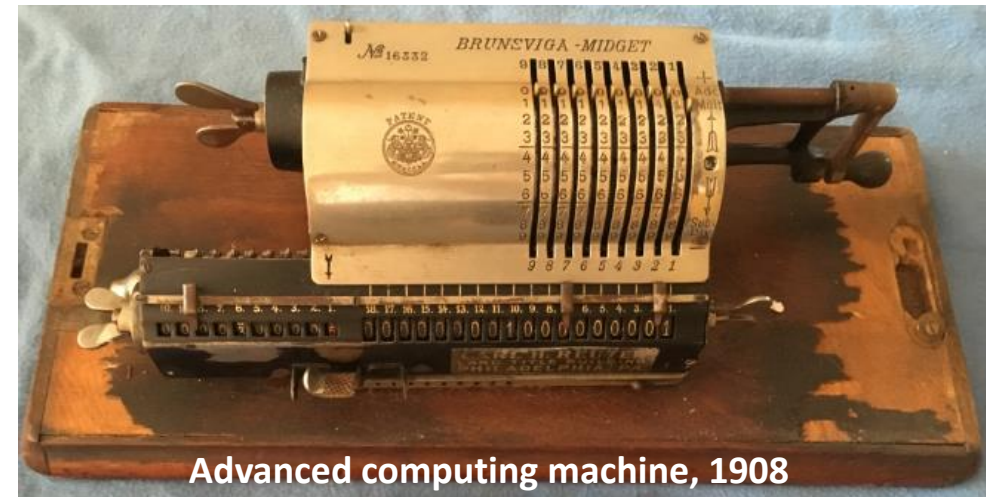
Notes for page 8 (next page)

- However, we just have two data points. Take the with/without treatment arms, and we have a 2x2 matrix.

- It may surprise you that We then use statistics developed to test beer samples in 1908.

- Here is what a top computer looked like back then…

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Assessing clinical trial success...

Time

	Before	After	
Without	534	689	change$_1$
With	520	605	change$_2$

Treatment arms

**Advanced computing machine, 1908**

Notes for page 10 & 11 (next pages)

- Let's take a step back – how do we measure anything, really? And the key is, something that changes in time?

- First q to ask is - how fast does it change??

- What's the shortest plausible change given biology?

- This is the question Nyquist answered almost 100 years ago and Fourier about 100 years before him!

Frequent measurements (blue dashes) reveal otherwise invisible physiology (gray line). Sparse sampling (time points A or B, circles) can lead to false predictions (thin dashed lines). Too frequent sampling (black dots) exposes noise in the measurement assay.

- Physiology = highly multidimensional space

- Health = highly multidimensional space

- Measuring continuous physiology = way to better and faster estimate trajectories; makes more sense if you imagine this as an N-dimensional plot

- Postulate: what we are able to measure reflects (imperfectly) on what we are not able to measure yet ("vertical excursions")

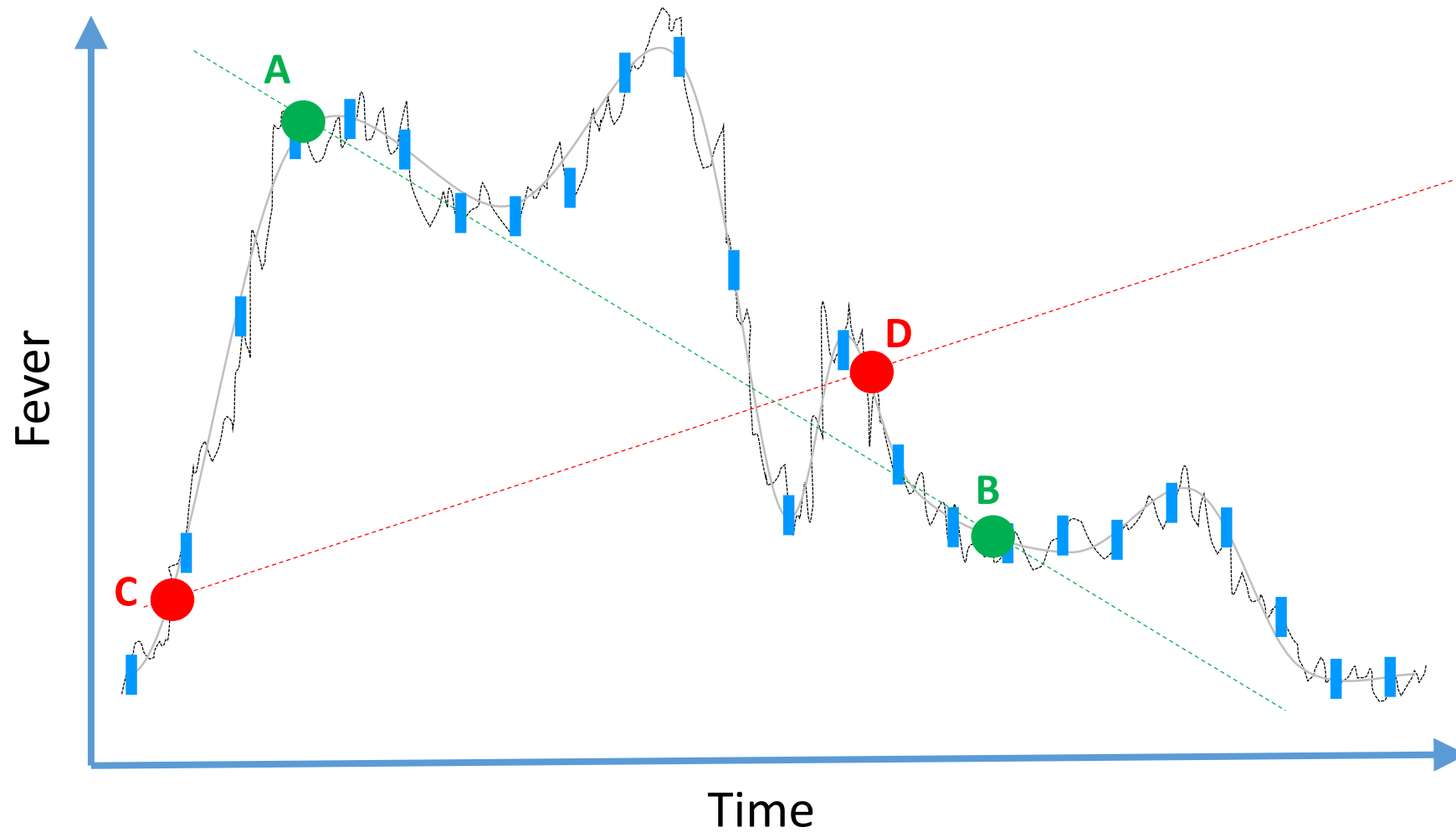# How do we measure anything? An old problem

"Real" Signal (invisible!)
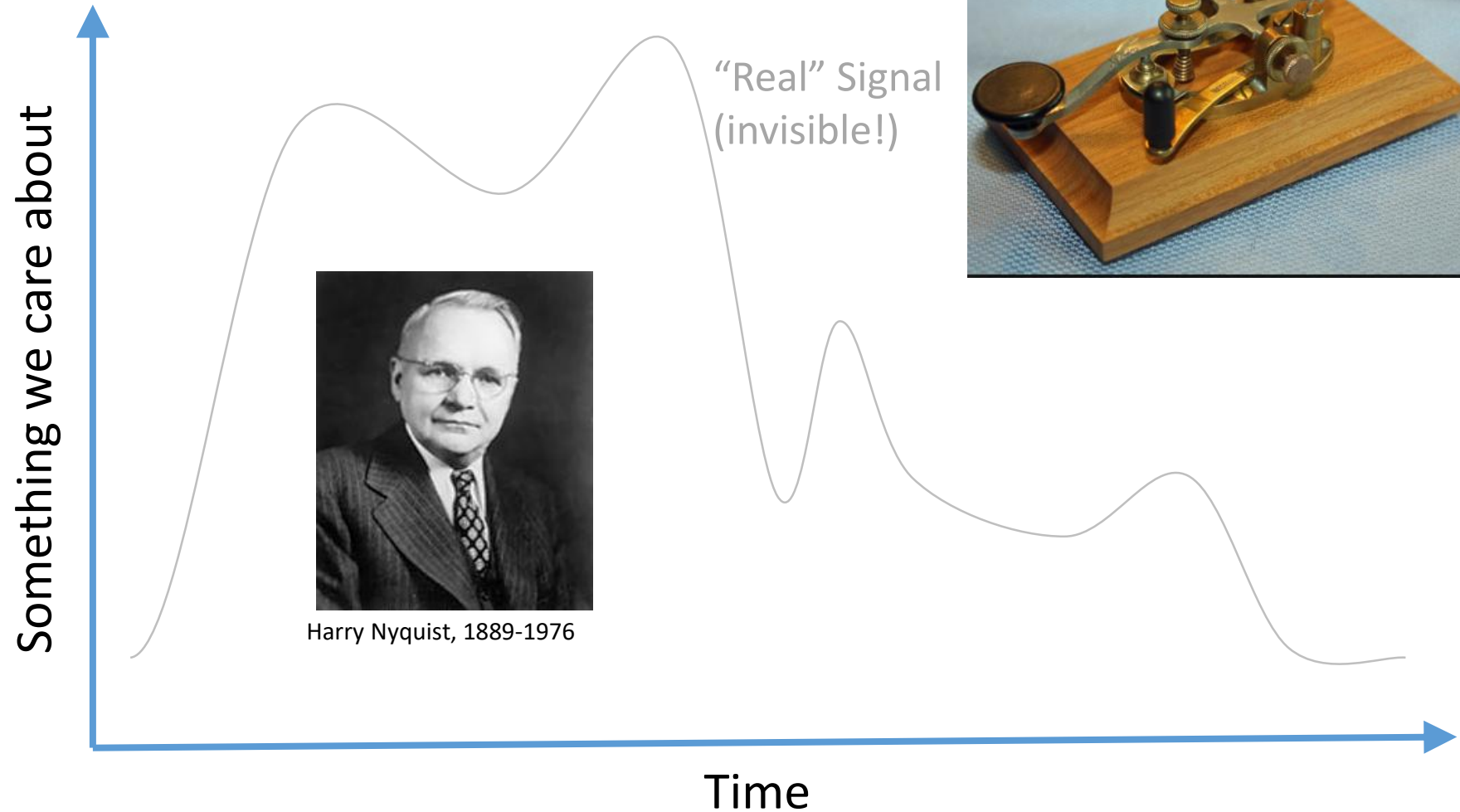
Harry Nyquist, 1889-1976
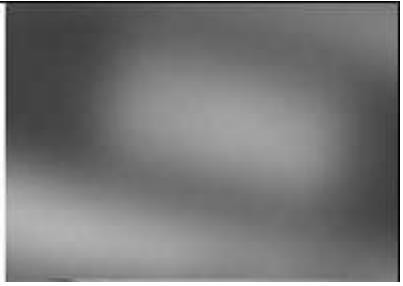
Joseph Fourier, 1768-1830

Something we care about

Time

# How do we measure anything? A solved problem

Problem of "under-sampling"

This typically doesn't work in the real world
Data lost is lost forever

Notes for page 14 & 15 (next pages)

- Imagine you are a detective helping solve a case. You review the security camera footage: 12.32, 12.34, 12.36 – boom. The apple has disappeared. What happened? Who did it?

- Now, would it not be nice to have more frames, more data to analyze?

- Well, help us by being a detective as we design better medicines!
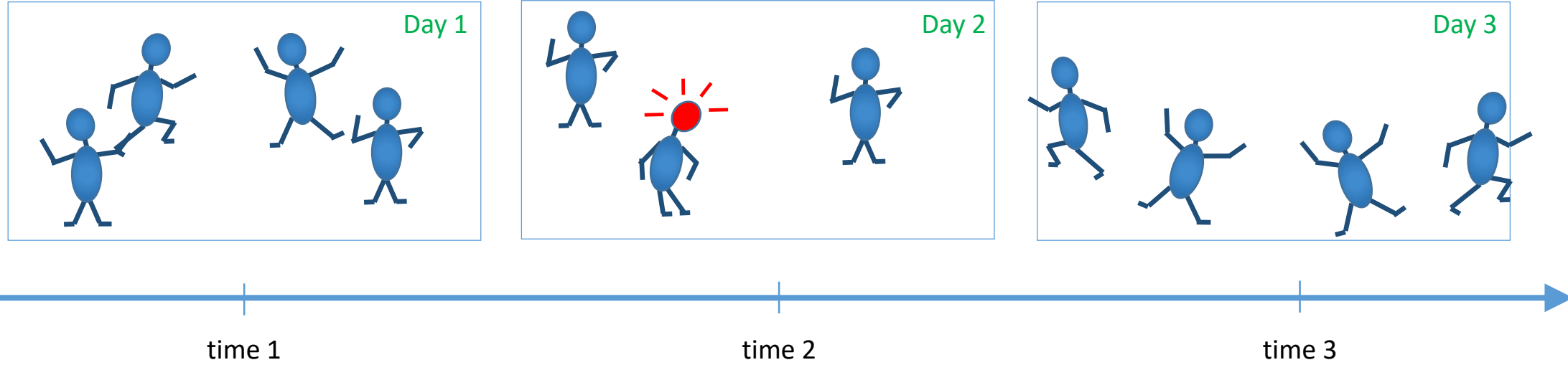
Security Camera Footage*

12:32

12:34

12:36
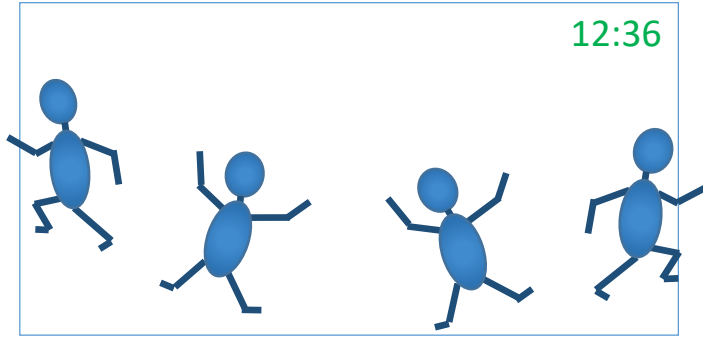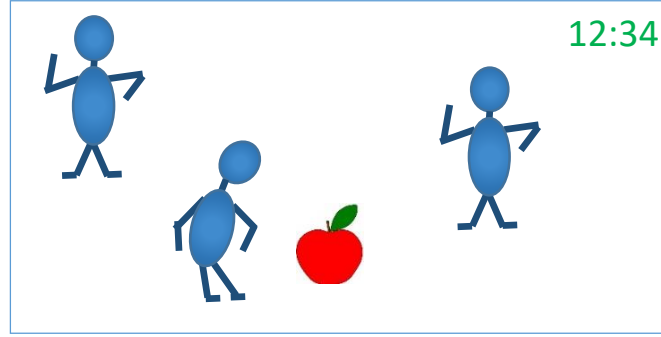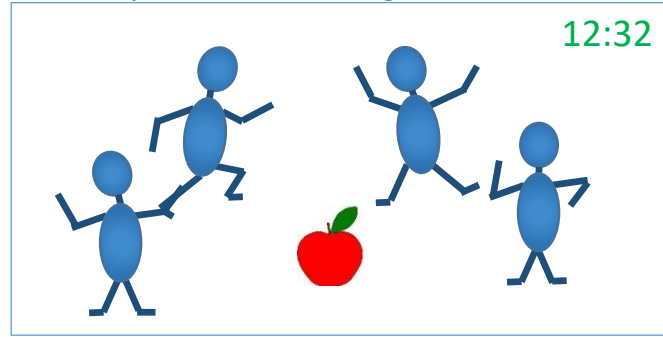
time 1

time 2

time 3

Apple reported missing in frame 3...
Would you rather have more frames & data to analyze?

Clinical Trial Scenario*

Day 1

Day 2

Day 3

time 1

time 2

time 3

Splitting headache on day 2…

*Would you rather have more frames & data to analyze?*

*simulated

Notes for page 17 (next page)

- To move the security camera scenario into something you care about: we can now get more data about your health and quality of life.

- Things like how you sleep. Do you have a fever? How do you talk? How do you move around? Are you fatigued? Stiff? In pain? How do you go about your daily life? What is your heart rate like?

- And all this, we can measure at every time point during the day and night.

- Now, when we test a new medicine, typically you would come into the clinic, say every Wednesday. But think about the security camera example – wouldn't it be better to have more data, to understand how YOU are doing the other days of the week?
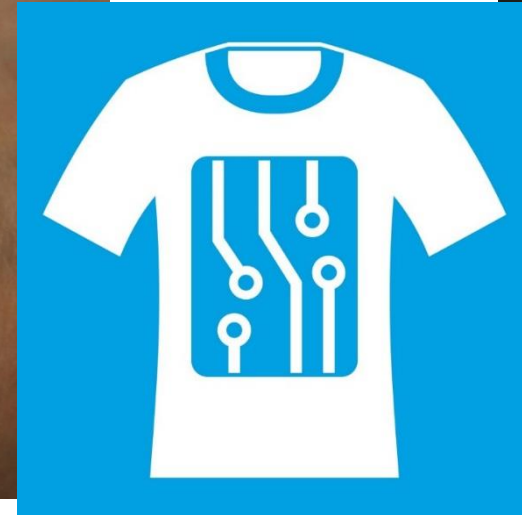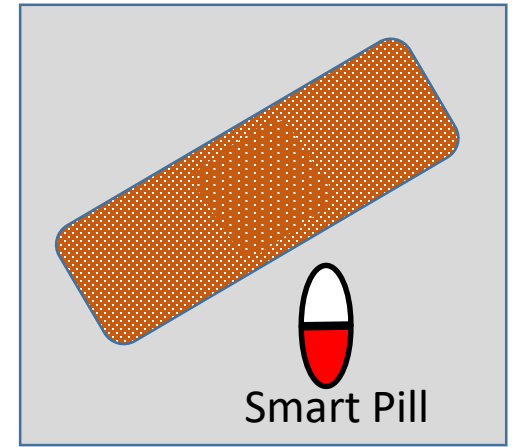
What is Continuomics?
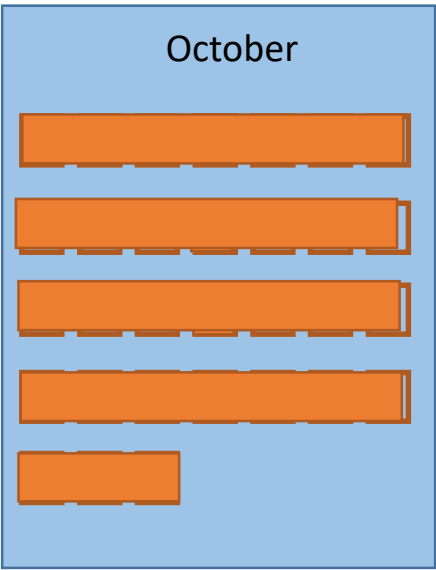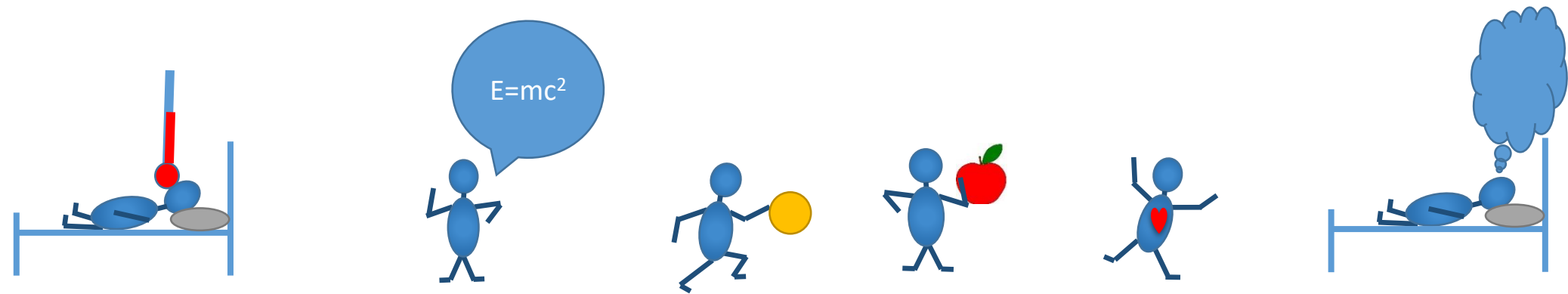
Notes for page 19 (next page)

- Lots of new devices are available right now to do that. Some may be as simple as a ring that measures your movements and heart rate. Others look like a wristwatch.

Lots of devices ("sensors") available

Smart Pill

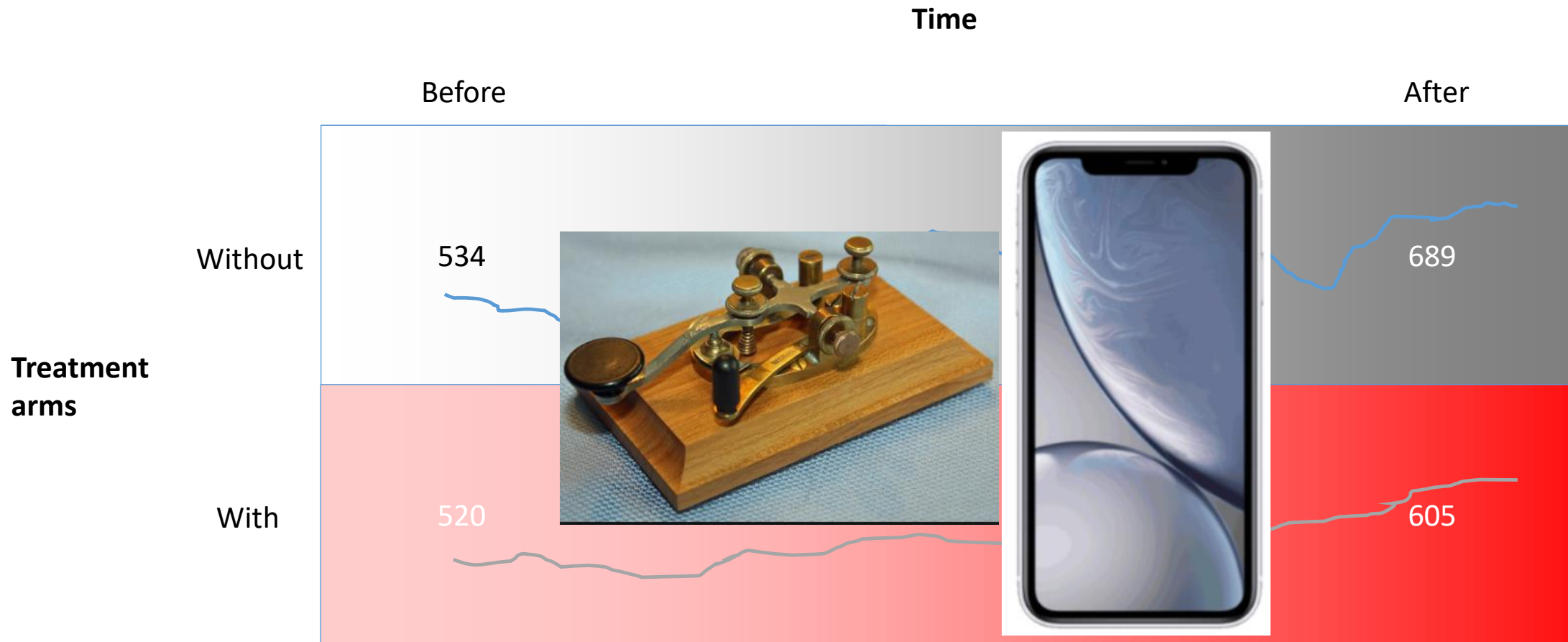83 BPM
82 BPM, 1m ago

Lilly

Notes for page 21 (next page)

Lilly

- This allows us to move past the two-by-two and stretch this table….

Nyquist - as basis of all modern communications even though he started with a telegraph, and couldn't imagine cell phones or the internet or voyager space probes Imagine where we can be with clinical research - imagine what **you** can do in this field!!

Next generation of clinical trials

Time

Before

After

Without   534   689

Treatment arms

With   520   605

Path over time is KEY!

1/19/2019   Company Confidential © 2017 Eli Lilly and Company   21

Towards the health dashboard

Health Trajectory

Overall activity

Sleep quality

Meds use

Temperature

Heart Rate

Blood Pressure

ECG: QT interval

Drug Therapy

Digital Therapy
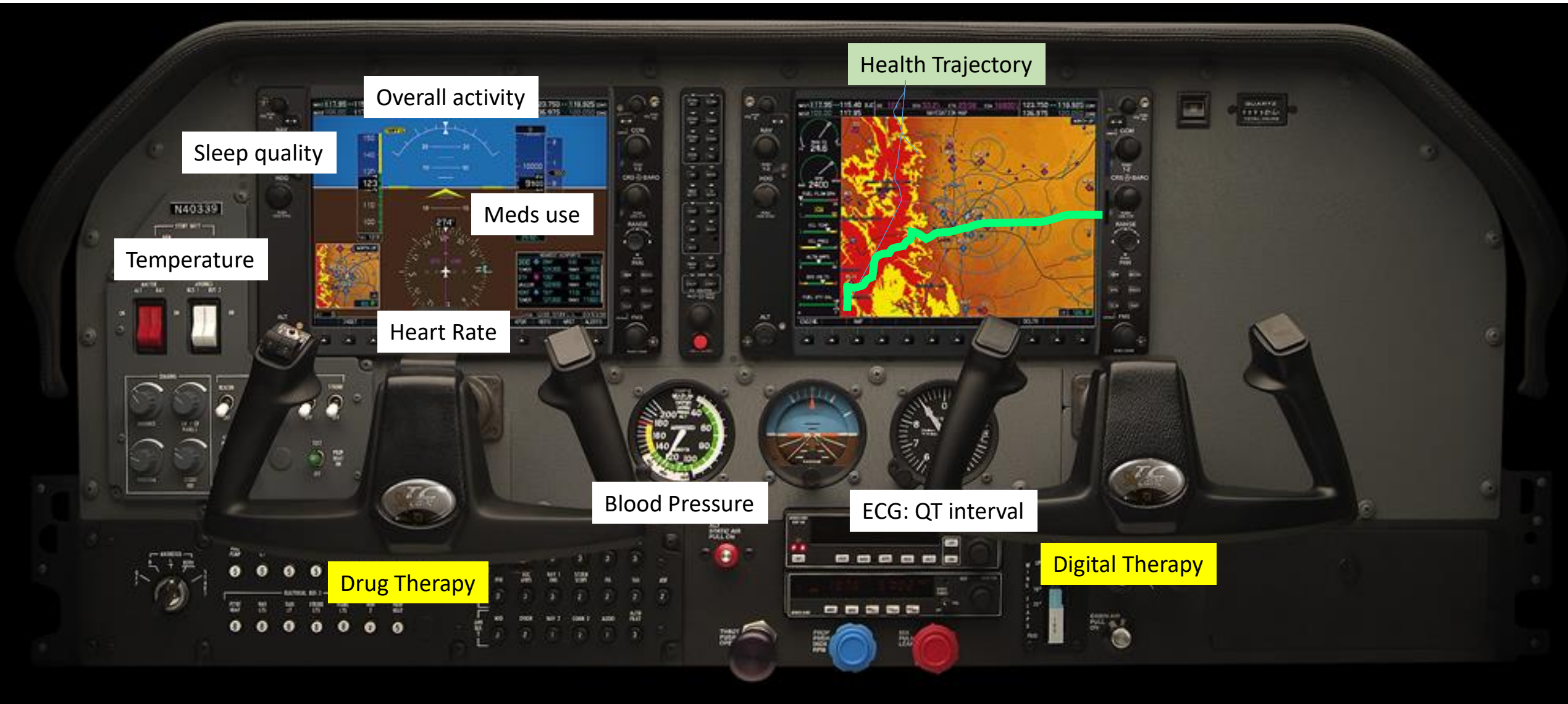
Notes for page 24 -25 (next pages)

- As opposed to exploratory efficacy endpoints

Continuomics – iCAN survey, 2018

Lilly

N = 13 parents, 31 iCAN *youth*
Vast majority **in favor** (12/13 parents and 30/31 youth)
Privacy is a concern (5/13 parents and 18/31 youth)
Form factor is critical(13/13 parents and 31/31 youth)

"I would avoid any device that is even more highlighting that my child is sick. The child has already to fight against the disease, then if we can avoid him not to be looked as a stranger in the street, this will make his life easier"

"EXTREMELY excited! It's about time!"

"I like it. I would feel safer that my child is being monitored and that the more data collected would make the out come safer for others use"

"It would be easy to keep track instead of writing it down and it would be more fun."

"The patients should be given a thorough and comprehensive explanation on what it truly means to have continuous data taken."

[I would not chose] "something that looks like a Holter monitor, bulky, with wires coming out of it"

"There are times that are mine and I don't want you to know"

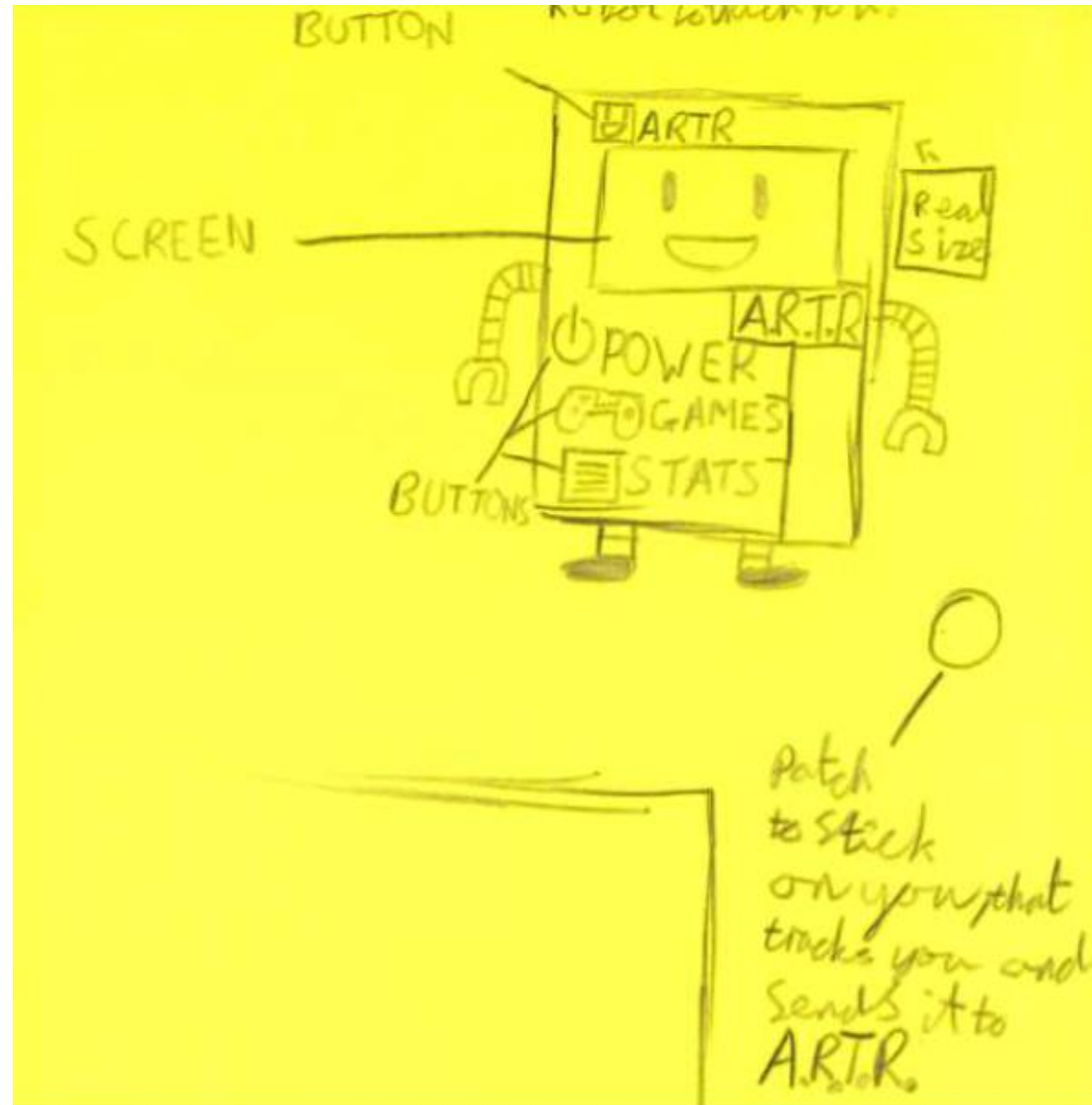"I would be comfortable with it as long as I knew exactly what would be captured and agreed with those measurements."

Continuomics – what young people say

"You don't understand me outside this clinical appointment"

"[the QoL questionnaire] does not reflect my life and what's important to me"

Aggregate opinion, UK pediatric rheumatology clinic

12 year old: Continuomics

Future Lilly scientist?

Roundtable discussions:

(1) General health based scenario

(2) Chronic disease based scenario (Diabetes)

(3) Serious or life-threatening disease based scenario (Cancer)

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General health based scenario

Adequate nutrition, physical activity and sleep are essential to health and growth in childhood.

- Physical activity in children and adolescence improves strength and endurance and builds healthy bones and lean muscles, develops motor skills and coordination, reduces fat and promotes emotional well-being. *The daily recommendation for physical activity for children age 6 years and older is 60 minutes per day.*

- Daily calorie needs are based on age, gender and physical activity level; for example, *males 14-18 years of age require between 2000-3,200 calories per day.*

- Children who get enough sleep have a healthier immune system, better school performance, behavior, memory and mental health. *Youth 6-12 years of age need 9-12 hours of sleep and teenagers need 8-10 hours.*

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Chronic disease based scenario (Diabetes)

Type 1 diabetes (T1D) is an autoimmune disease in which insulin-producing beta cells in the pancreas are mistakenly destroyed by the body's immune system. Its causes are not fully known, and there is currently no cure.

People with T1D are dependent on injected or pumped insulin to survive. If not treated properly, people with T1D are vulnerable to health issues ranging from minor to severe.

Most people with T1D spend the majority of their time with blood-glucose levels outside the recommended healthy range, which can lead to potentially deadly episodes of hyperglycemia (high blood sugar) and hypoglycemia (low blood sugar).

Chronic high blood sugar often causes devastating health complications later in life, including blindness, kidney failure, heart disease and nerve damage that can lead to amputations.

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Serious or life-threatening disease based scenario (Cancer)

Cancer is a group of many related diseases that are characterized by abnormal cells that that grow rapidly and can damage or destroy normal body tissues and spread to other parts of the body.

While the causes of cancer are largely unknown, it is more common in older people than children and is considered a serious and potentially life threatening disease.

Fortunately, cancers can be treated and some cancers can be cured. For those that are not cured with currently available treatments (surgery, radiation, chemotherapy, stem cell transplants, and/or targeted therapies), new therapies are being developed.

However, therapies have potential side effects such as nausea, hair loss, abnormal blood cell counts, and infections that need close monitoring while the patient is on treatment.

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Roundtable Activity

- Complete your worksheet

- Discuss with your group the device that you most prefer and why

- Discuss with your group the device you least prefer and why

- Prepare to have a representative from your group share your discussion to the larger group

Lilly

"Continuomics"

Please complete the following:

Age:
- ☐ Younger than 12 years old
- ☒ 12-18 years old
- ☐ Older than 18 years old
- ☐ Parent

Gender: _____**Female**_____

Region:
- ☐ North America
- ☒ Outside North America

Scenario 1: General Health

Adequate nutrition, physical activity and sleep are essential to health and growth in childhood. Physical activity in children and adolescents improves strength and endurance, builds healthy bones and lean muscles, develops motor skills and coordination, reduces fat, and promotes emotional well-being. *The daily recommendation for physical activity for children 6 years and older is at least 60 minutes per day.* Daily calorie needs are based on age, gender and activity level; fo*r example, males age 14 – 18 require between 2,000 and 3,200 calories per day.* Children who get enough sleep have a healthier immune system, and better school performance, behavior, memory, and mental health. *Youth 6-12 need 9-12 hours of sleep and teenagers need 8-10 hours.*

On a scale of 1-5, how do you feel about using continuous recording (assuming ideal device) for maintaining a healthy life style? (Circle a number)

1   2   3   (4)   5

Very uncomfortable   Very comfortable
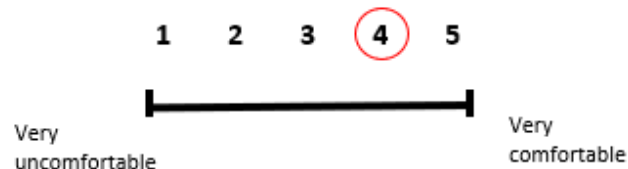
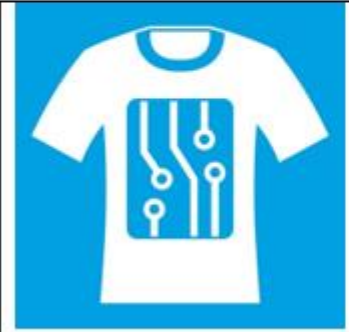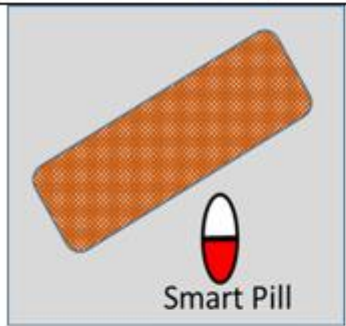Tell us why you like or don't like continuous recording –

The monitoring would tell me if I am being active enough each day. If I am not being active enough I could go play basketball with my friends.

Instructions:

1. Rank the following devices in order from 1-5.
   1 = Most preferred,..., 5= Least preferred. For 1 and 5 only, please tell us why this was your least and most preferred device.
2. Please share your thoughts on the options during the table discussion.

	# __2___ (← enter rank) _____ _____ _____		# __5___ (← enter rank) I would not want to wear a t-shirt because it might be very noticeable to others.
Smart Pill	# __4___ (← enter rank) _____ _____ _____		# __1__ (← enter rank) Many people have watches so you would not really know that I am measuring my health.
	# __3___ (← enter rank) _____ _____ _____	Other thoughts to share around these devices– For the other devices, how would you view what is being measured?	

Group Readout

- State which scenario did your group discuss
- State which device the group preferred and why
- State which device the group least preferred and why

POSTER ACTIVITY

1. Consider each health scenario (healthy, chronic condition, serious health condition)
2. Determine your level of comfort in the use of continuous data collection for that health scenario
3. Mark your selection on the poster with a sticker for each of the health conditions.
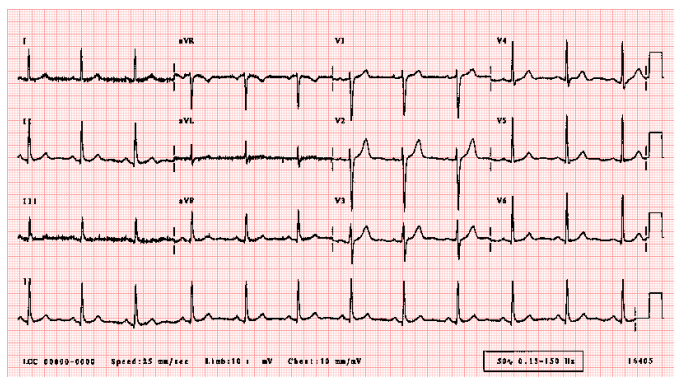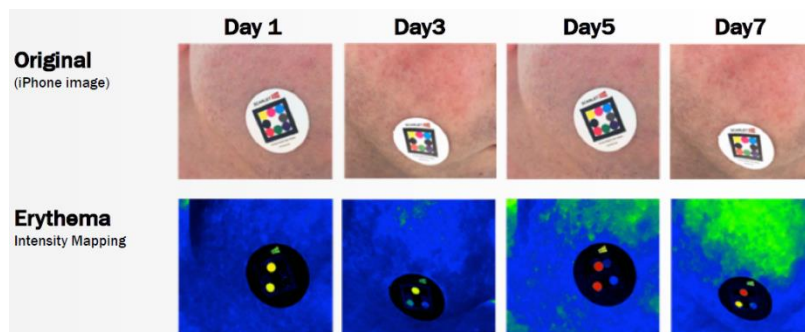
Thank you for participating!
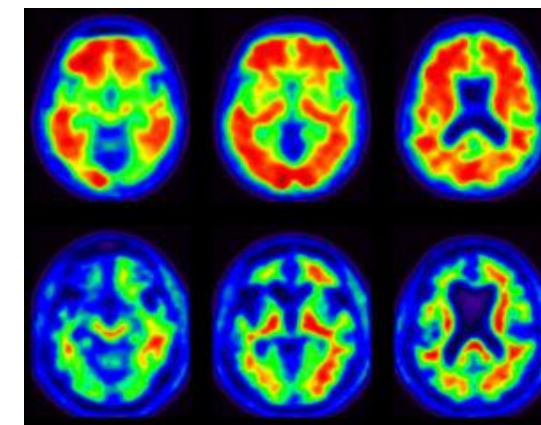
Thank you!

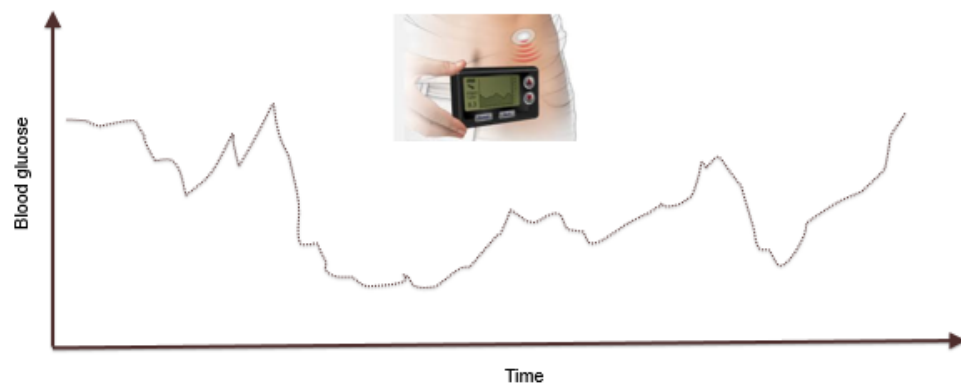# Adapt sampling to frequency of physiology

ECG: ms - s

Skin imaging: days

Amyloid: months

Glucose: minutes

~11 orders of magnitude!
ECG: 10^{-3}s
Glucose: 10^2s
Skin Imaging: 10^5s
Amyloid PET: 10^7s
DEXA: 10^8s

DEXA: years