



DH06 - Digital Biomarkers Touch Down in Statistical Programming



**PHUSE EU Connect 2020 –
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Digital Biomarkers

Definition and Examples

Digital Biomarkers are:

“characteristics [...] that are objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention”

“Digital refers to the method of collection as using sensors and computational tools”¹



Summary of current technologies for monitoring health/performance and targeted physical measurements.
<https://www.frontiersin.org/articles/10.3389/fphys.2018.00743/full>



Verification of digital Biomarkers

Verification – Analytical Validation – Clinical Validation²

In order to use indicators, derived from devices for submission purposes, not only the device, but also the indicator has to be fit for use and validated

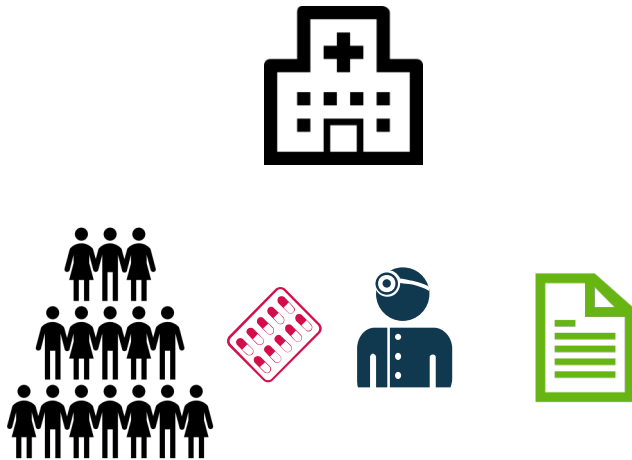
Different levels of validation exist, not all fit for clinical decision making

Parameters	Units	Sampling rate	Validation Status
RSSI - Received Signal Strength Indicator	dBm	0.25Hz	N/A
Accelerometer (X)	mG	50Hz	FDA 510k
Accelerometer (Y)	mG	50Hz	FDA 510k
Accelerometer (Z)	mG	50Hz	FDA 510k
Respiration rate - calculated on-board device	BrPM	0.25Hz	FDA 510k
Respiration Rate	BrPM	1/min	FDA 510k (submitted)
R-R interval - calculated on-board device	msec	Variable	FDA 510k
1 Min Average Heart Rate	BPM	1/min	FDA 510k
Posture Identifier - Categorical	N/A	1/min	Validated
Torso Tilt Angle	Degrees	1/min	Validated



Traditional clinical studies

On-Site measurements

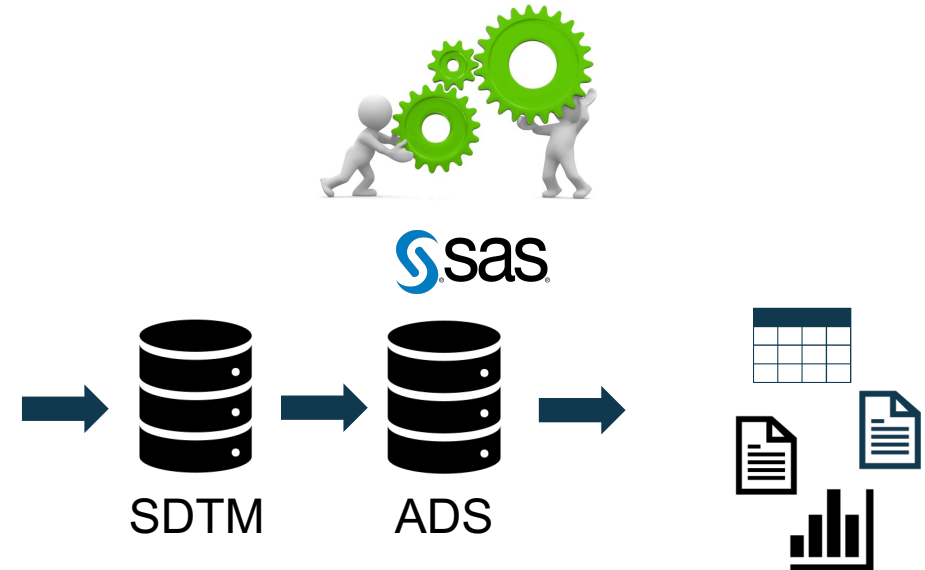


Clinical Database



SDTM/ ADAM transformation

Generation of TLF





New technologies come into play

Remote device measurements



Cloud/ Big Data Solutions



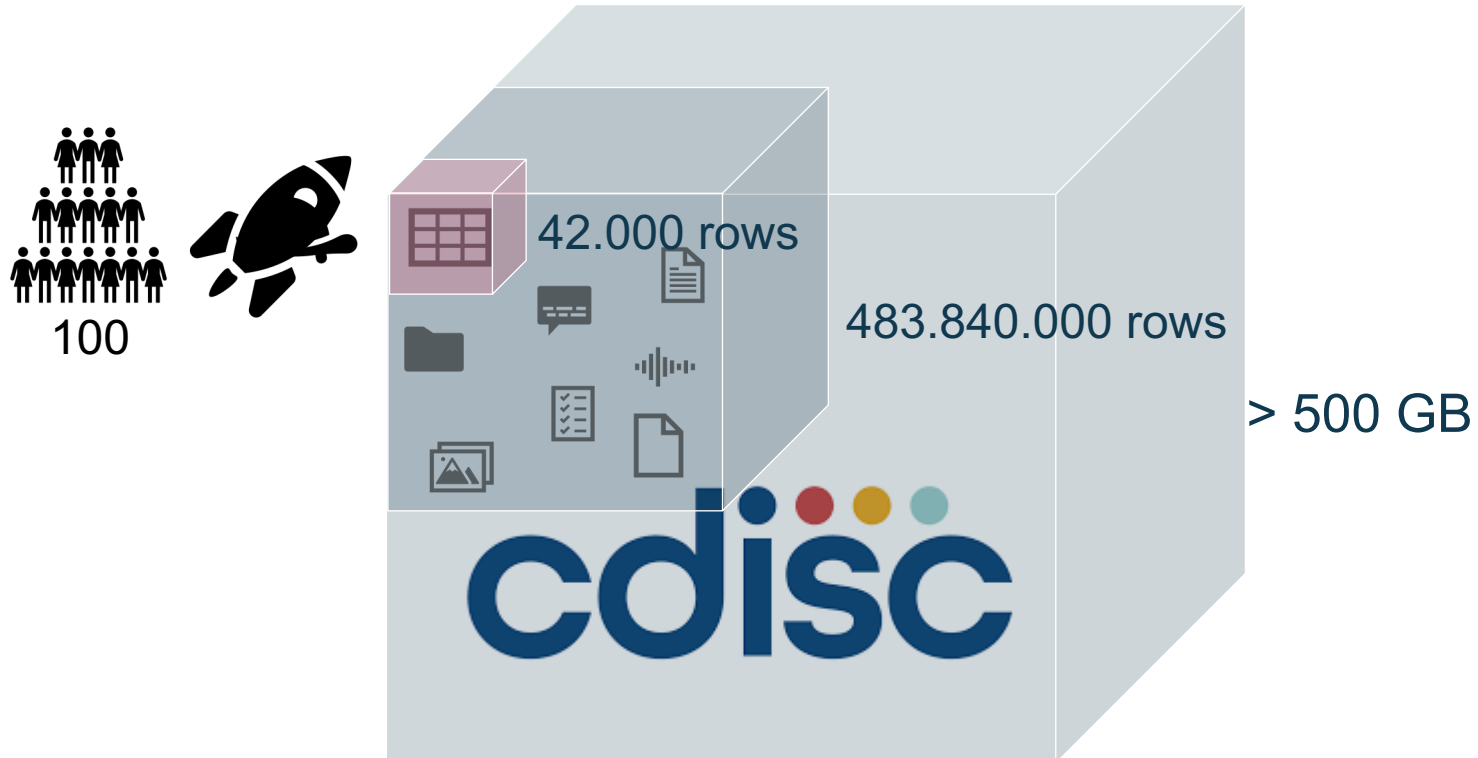
Analytics and reporting





Volume, velocity, veracity

Traditional (7 Days, 10 obs. /day)
Continuous, high resolution (7 Days, 125hz)
Standardization

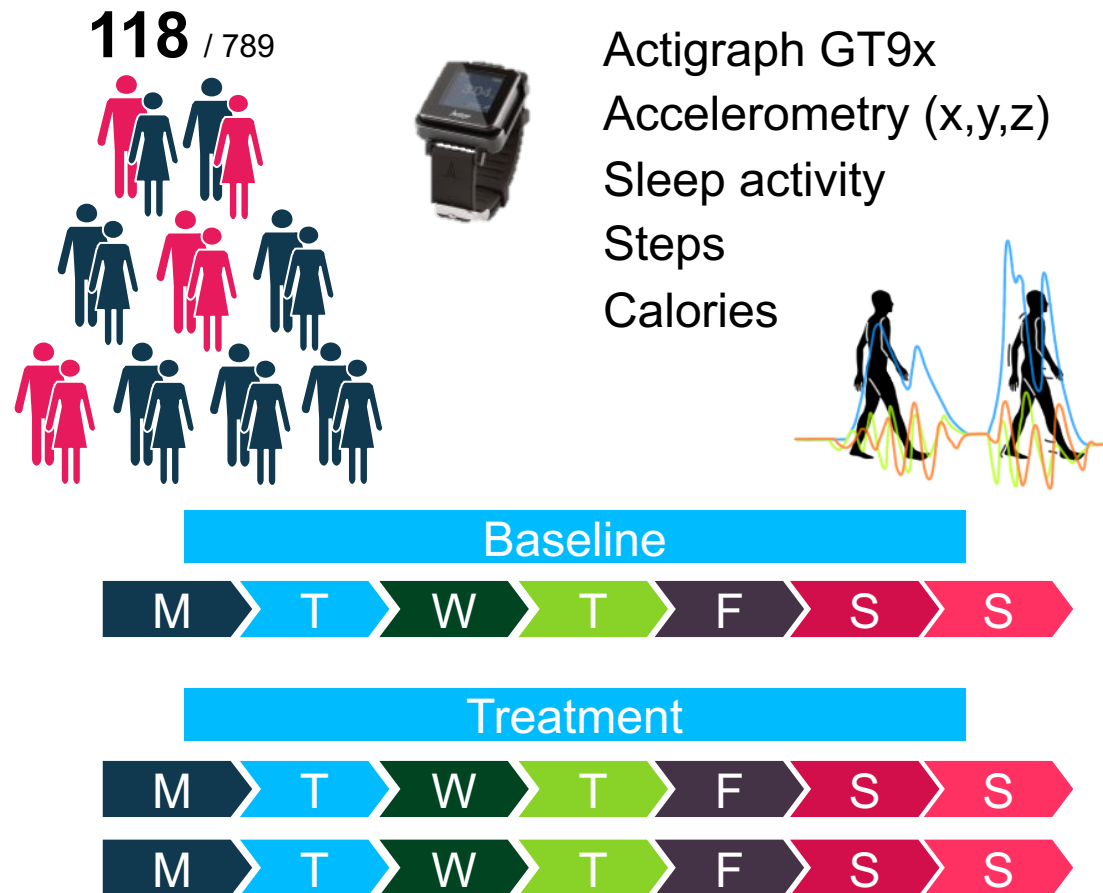




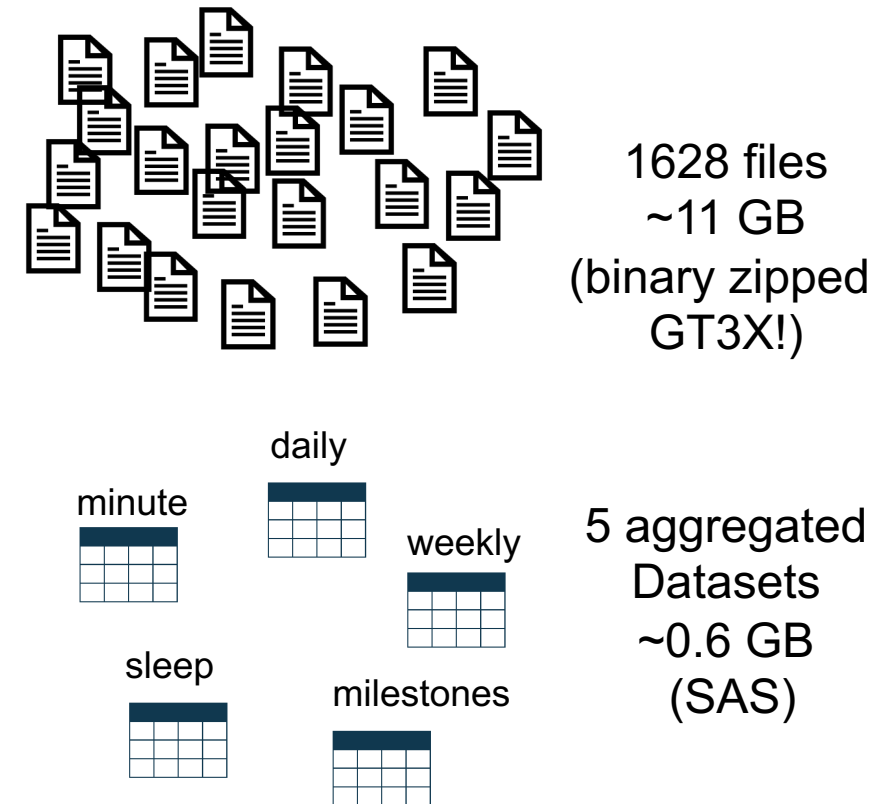
Disclaimer: The following represents insights gained during an explorative analysis of device data from a clinical trial around heart failure patients. The analysis is ongoing and all results are pending.

Digital Biomarker Data in Action

Study Design



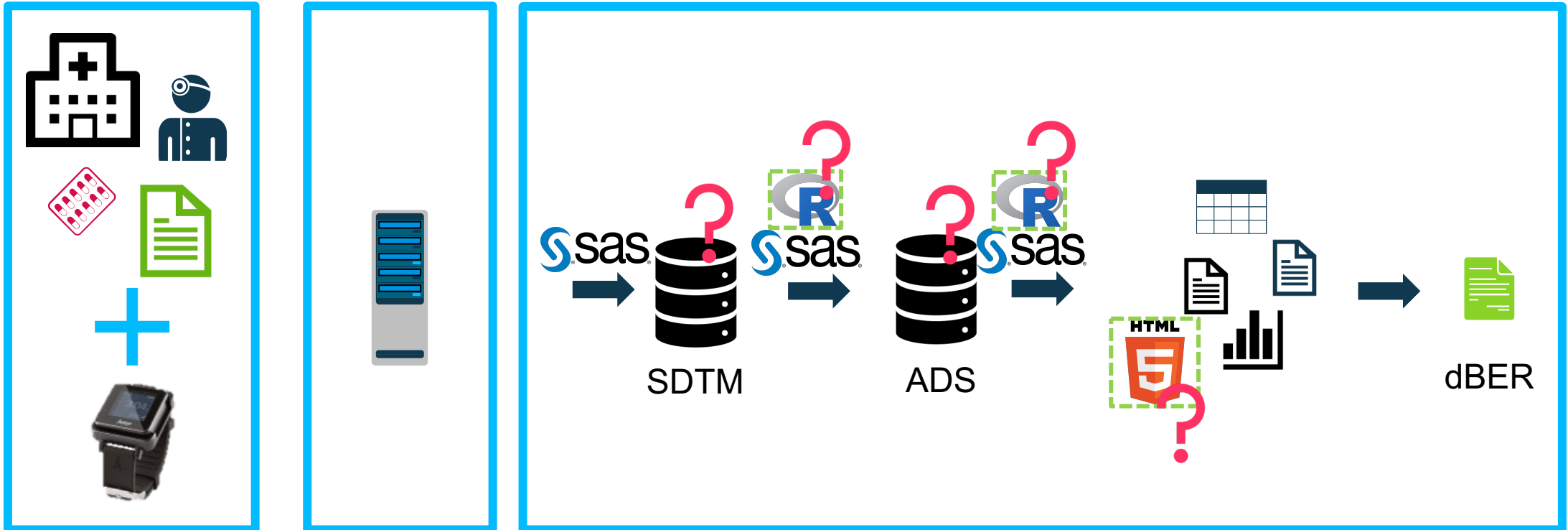
Data

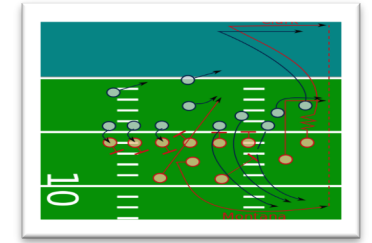


Digital Biomarker Data in Action



f1





f2

cdisc

phuse



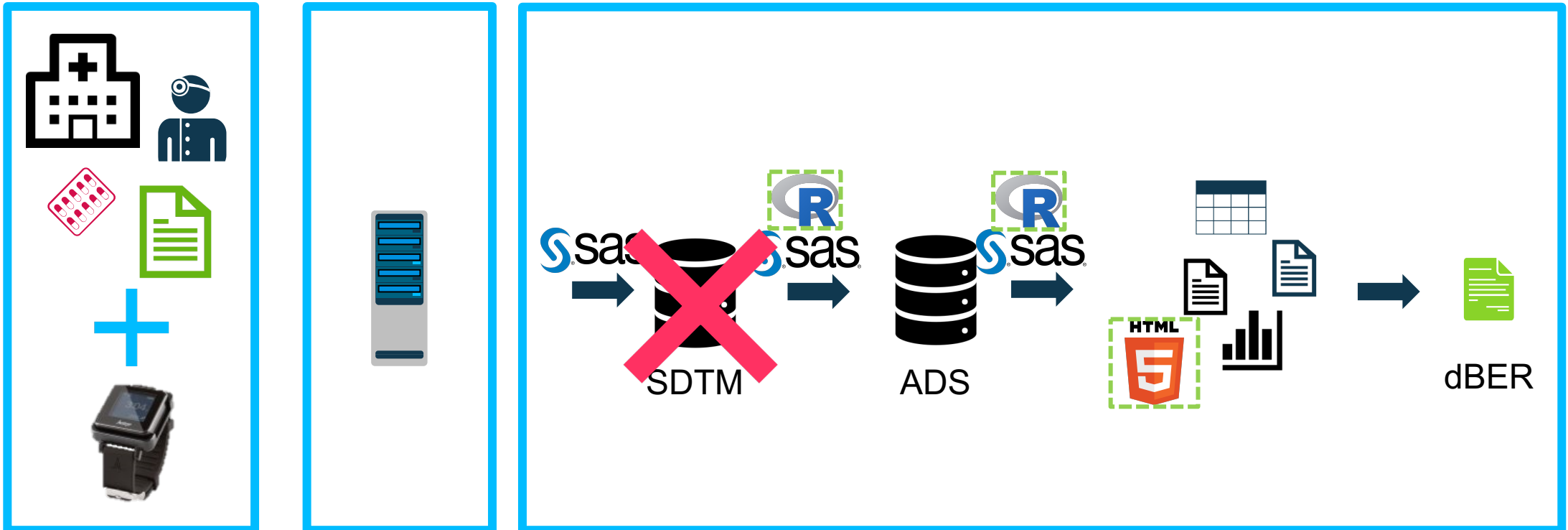
NOTHING!*

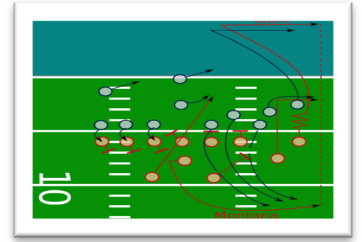
* One great PHUSE paper about SDTM from NovoNordisk³

Digital Biomarker Data in Action



f1





f2

„A BDS dataset contains one or more records
per subject, per analysis parameter, per analysis timepoint.“ [Adam IG 1.2]⁴

Traditional clinical data

Data collection at visit

Storage of measured single
variables at this certain timepoint



Digital biomarker data

Data collection ongoing in
a specified timeframe

Single values e.g. to summarize
patterns per wearing period

Hierarchical Structure of data



ADS - Activity Data



f3

Activity

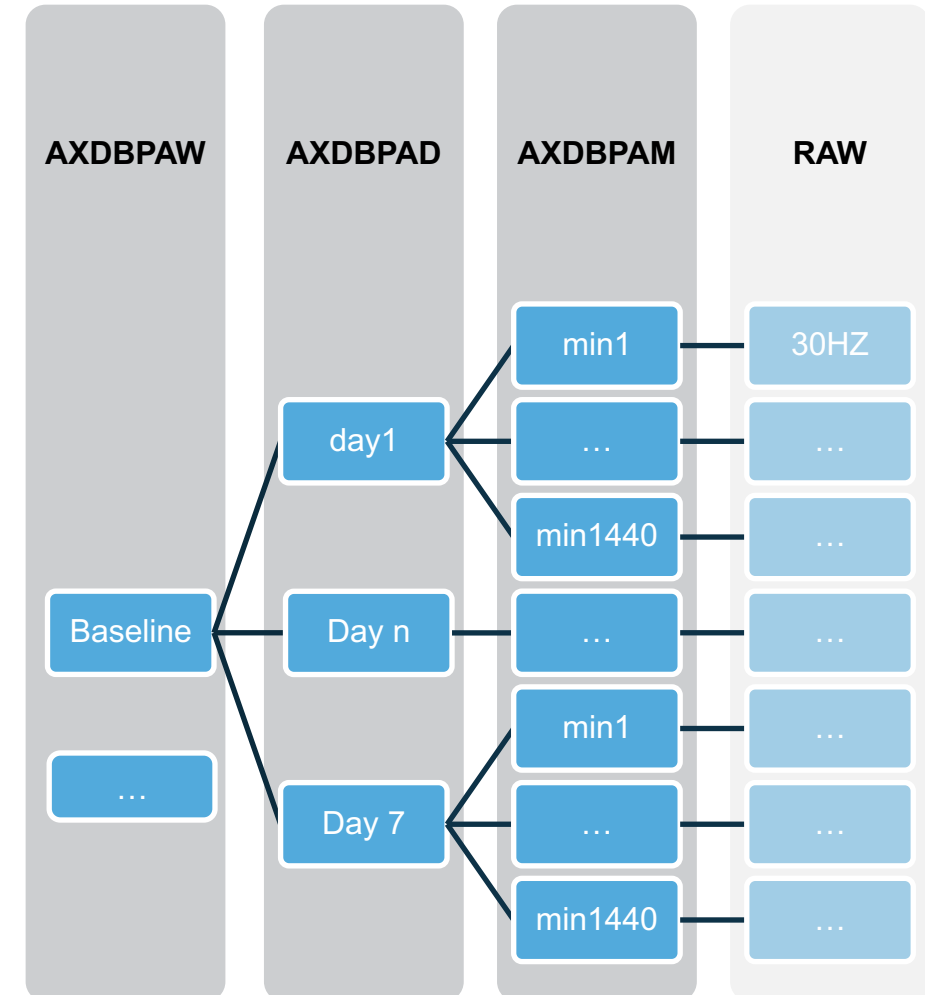
“the situation in which a lot of things are happening or people are moving around” [CambridgeDict]⁵

Derived based on x, y, z counts measured by an accelerometer

Different aggregation measures may be appropriate for different questions

This results in different digital biomarkers reflecting a certain level of aggregation

Analysis (X) Digital Biomarker Physical Activity
[Aggregation Level(**W**eekly, **D**aily, **M**inute)]





ADS - Activity Data – Param and Aval



f4



Steps



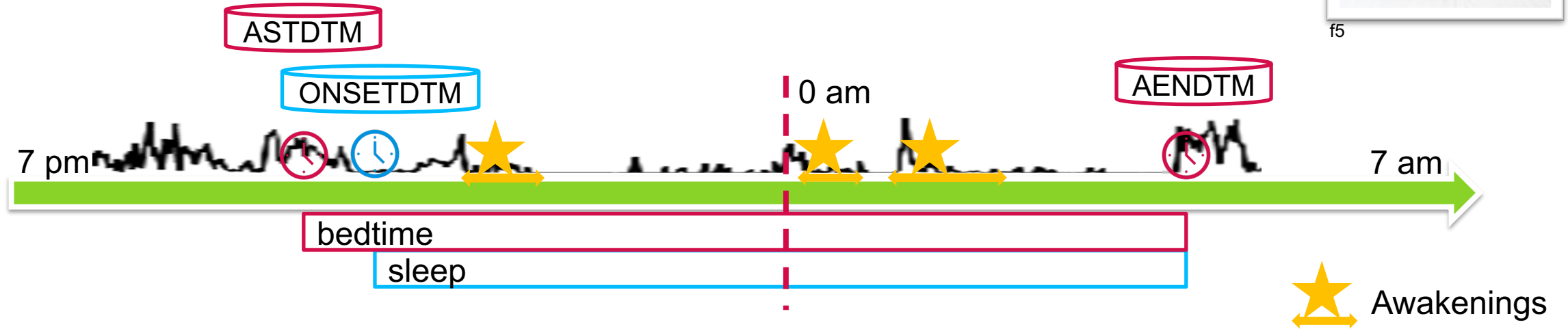
Activity



Based on Fredson 98

MET = metabolic equivalent of task

ADS - Sleep Data

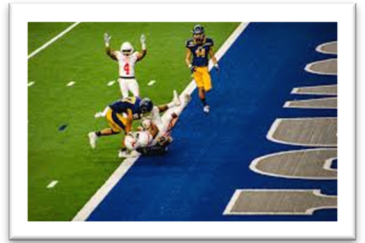


PARAMCD	AVAL
AWAKECNT - The number of awakenings during the sleep period	3.00000000
AWAKEMIN - The total number of minutes marked as awake during the sleep period	22.00000000

Analysis (X) Digital Biomarker Physical Activity Sleep Data (AXDBPASL)

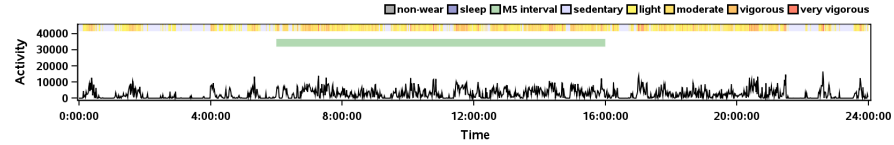


Visualization

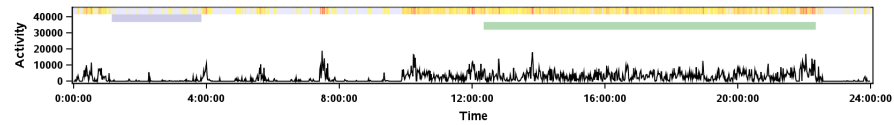


f6

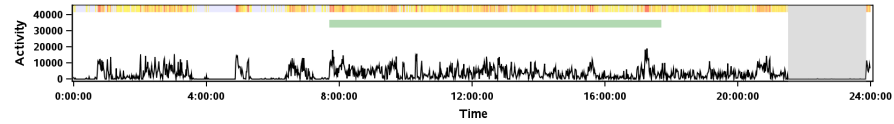
Day 1 of visit 2 (Wednesday 13MAR2019)



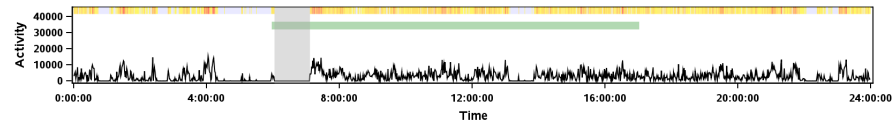
Day 2 of visit 2 (Thursday 14MAR2019)



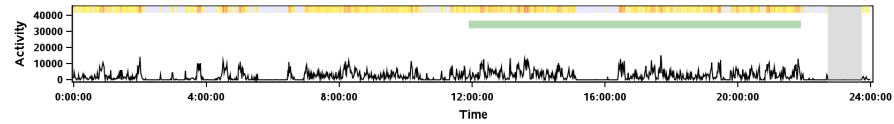
Day 3 of visit 2 (Friday 15MAR2019)



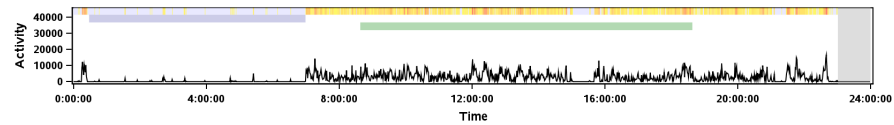
Day 4 of visit 2 (Saturday 16MAR2019)



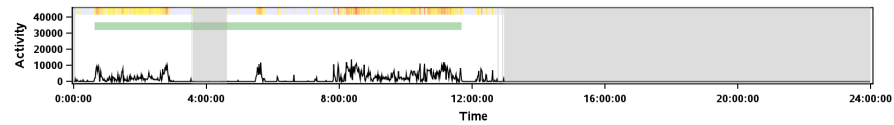
Day 5 of visit 2 (Sunday 17MAR2019)



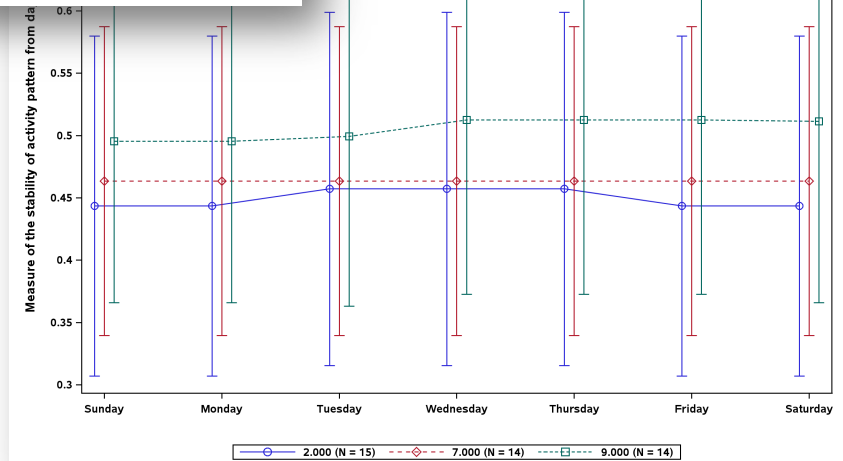
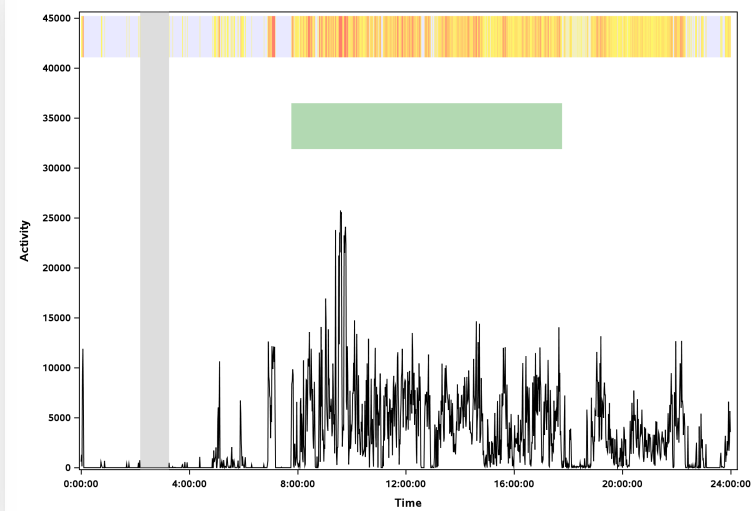
Day 6 of visit 2 (Monday 18MAR2019)



Day 7 of visit 2 (Tuesday 19MAR2019)



Activity of subject 100010001 on day 1 of visit 2 (Wednesday 12DEC2018)



Summary

Research

Differences

ADS based
on
aggregation

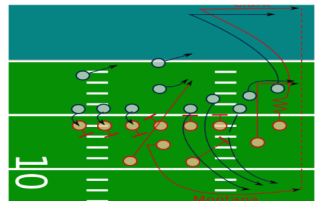
Activity

Sleep Data

Visualization



f1



f2



f3



f4



f5



f6

Data problems occurred

Data issues
Unknown Subjects
Artifacts
Queries

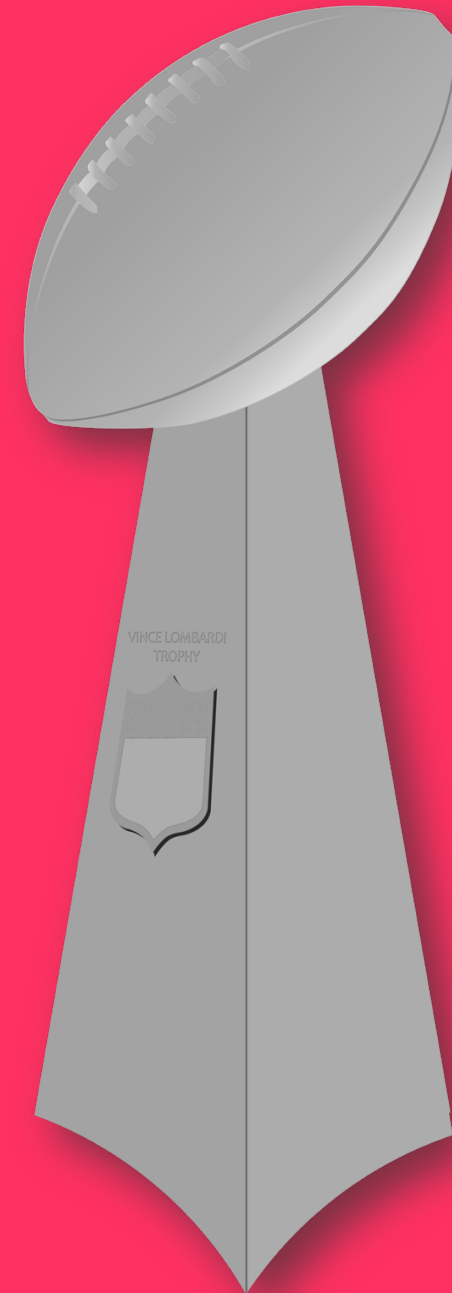
Device IDs not unique

Parameter definitions



<https://commons.wikimedia.org/wiki/File:OklahomaSooners-IdahoStateBengals-Tackle.jpg>

Further Challenges





Contact us



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Special thanks to the study team:

Mercedeh Ghadessi (Bayer AG)

Maike Ahrens (Chrestos Concept GmbH)

Roland Meizis (Chrestos Concept GmbH)





Resources

¹<https://www.nature.com/articles/s41746-019-0090-4>

²<https://www.nature.com/articles/s41746-020-0260-4>

³<https://www.lexjansen.com/phuse/2019/rw/RW03.pdf>

⁴[https://www.cdisc.org/system/files/members/standard/foundational/adam/ADaMIG v1.2-Final.pdf](https://www.cdisc.org/system/files/members/standard/foundational/adam/ADaMIG_v1.2-Final.pdf)

⁵<https://dictionary.cambridge.org/us/dictionary/english/activity>



Resources - Pics

[f1https://commons.wikimedia.org/wiki/File:Cowboys_huddle.jpeg](https://commons.wikimedia.org/wiki/File:Cowboys_huddle.jpeg)

[f2https://commons.wikimedia.org/wiki/File:NFL_1982_The_Catch.svg](https://commons.wikimedia.org/wiki/File:NFL_1982_The_Catch.svg)

[f3https://commons.wikimedia.org/wiki/File:Aaron_Rodgers_-_January_2,_2011_2.jpg](https://commons.wikimedia.org/wiki/File:Aaron_Rodgers_-_January_2,_2011_2.jpg)

[f4https://www.oregonlive.com/nfl/2018/12/watch-kansas-citys-patrick-mahomes-throws-incredible-no-look-pass.html](https://www.oregonlive.com/nfl/2018/12/watch-kansas-citys-patrick-mahomes-throws-incredible-no-look-pass.html)

[f5https://www.mattressadvisor.com/nfl-teams-people-lose-sleep/](https://www.mattressadvisor.com/nfl-teams-people-lose-sleep/)

[f6https://commons.wikimedia.org/wiki/File:Touchdown_--_Texas_High_School_vs_Highland_Park_High_School_first-round_playoffs.jpg](https://commons.wikimedia.org/wiki/File:Touchdown_--_Texas_High_School_vs_Highland_Park_High_School_first-round_playoffs.jpg)