# SMART TRIALS: MOVING FROM SITE-CENTRIC TO PATIENT-CENTRIC CLINICAL TRIALS


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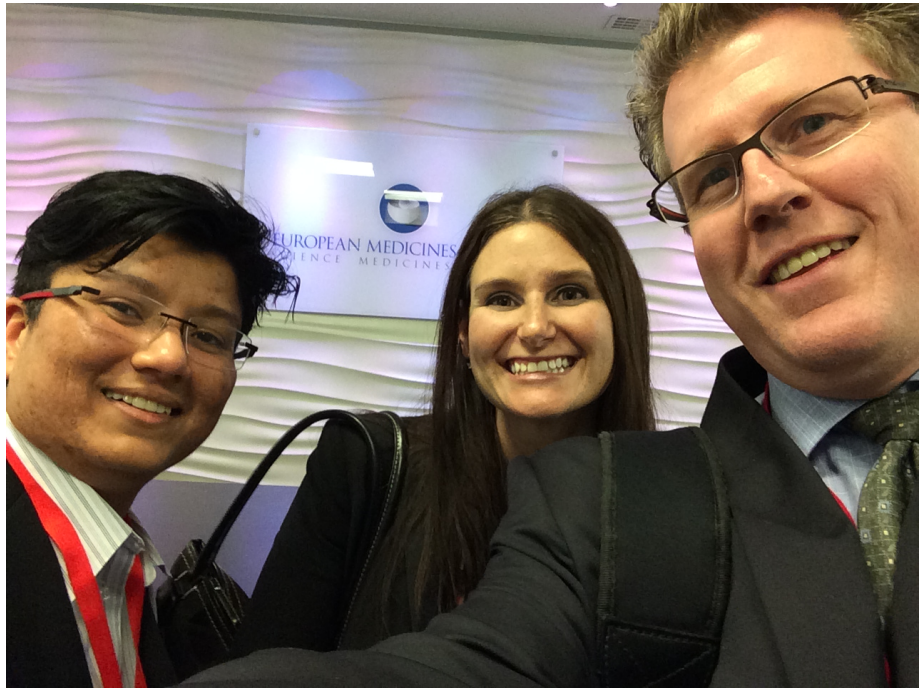
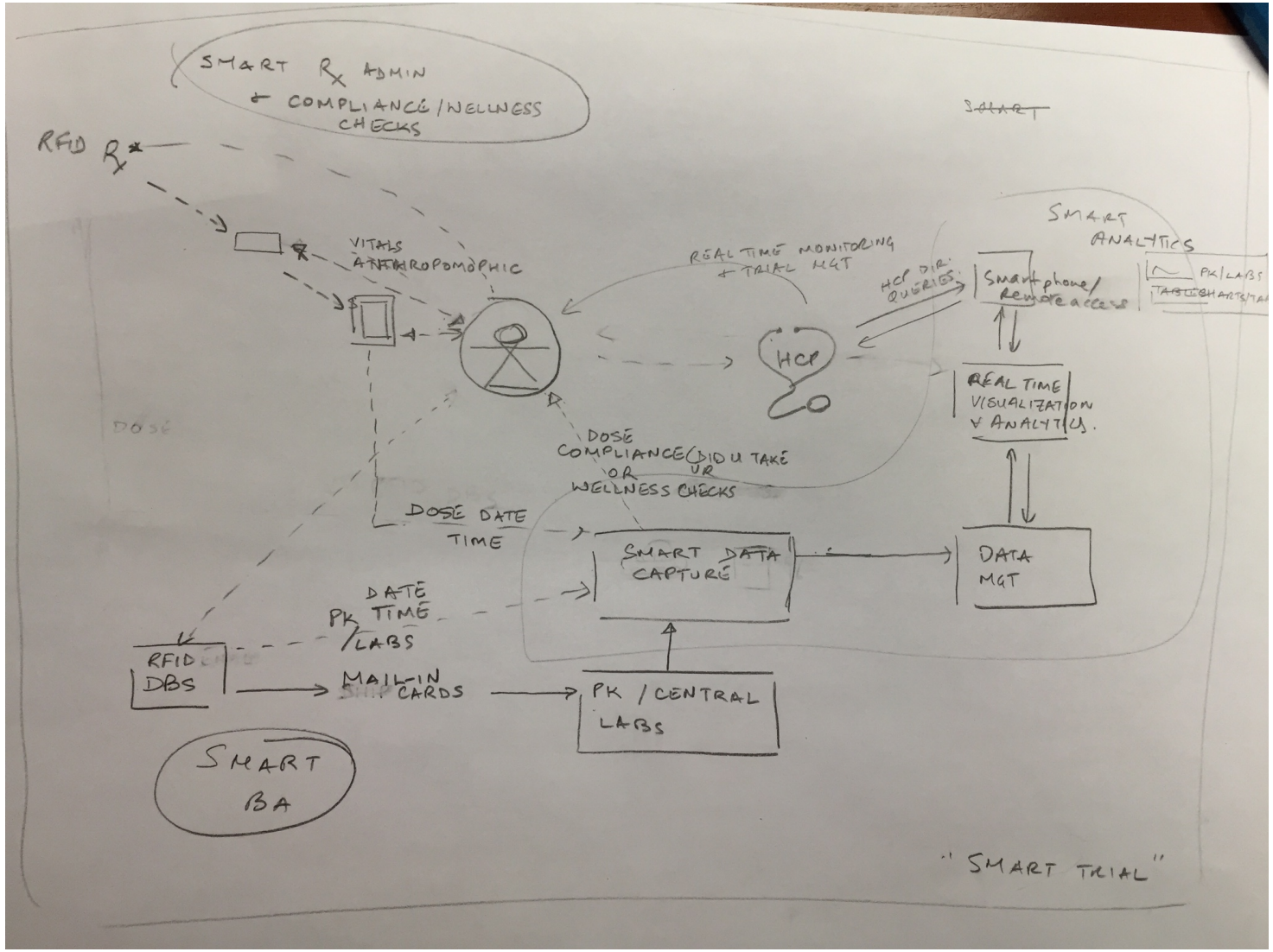
EBF Open Symposium

# The Birth of the Smart Trials Project at Merck




Successful Presentation to the European Medicines Agency in 2014 on the use of DBS in a Phase III Clinical Program



# The Current Clinical Trial Paradigm Needs Transformation

## Site-centricity

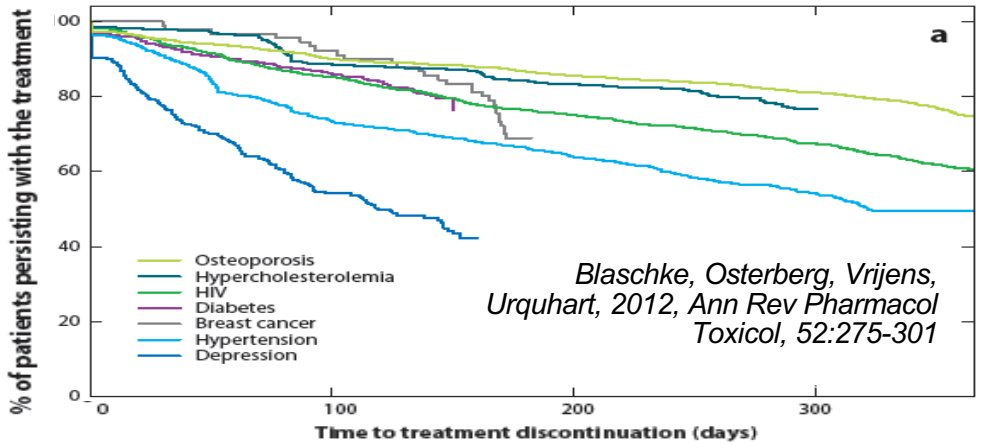
- Patient recruitment often limited to those that live near clinical site
- Patient and family burden
- Static “snapshots” of data
- High cost for each visit
- Limited feedback of data during the study

## Operational Inefficiencies

- Transcriptional errors
- Laborious data acquisition, reconciliation, & integration
- Cost of visits

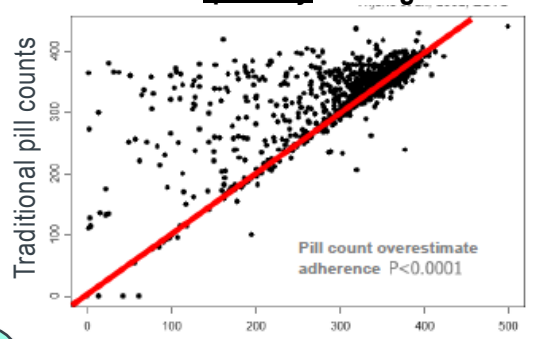
**Current paradigm does not take advantage of emerging trends in digital health technologies that can drive a more patient-centric approach**

## Adherence & Data Inaccuracies




*Blaschke, Osterberg, Vrijens, Urquhart, 2012, Ann Rev Pharmacol Toxicol, 52:275-301*

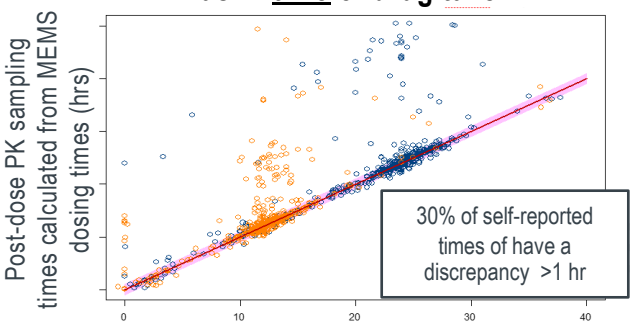
**Bias in quantity of drug taken**




Tablet counts based on electronic monitoring

*Vrijens et. al. 2002, ECTS*

**Bias in time of drug taken**




Post-dose PK sampling times calculated from patient-reported dosing times (hrs)

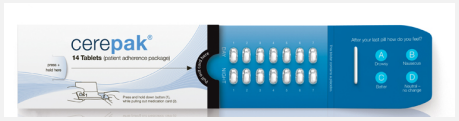
*Tousset. et. al. 2005, PAGE*

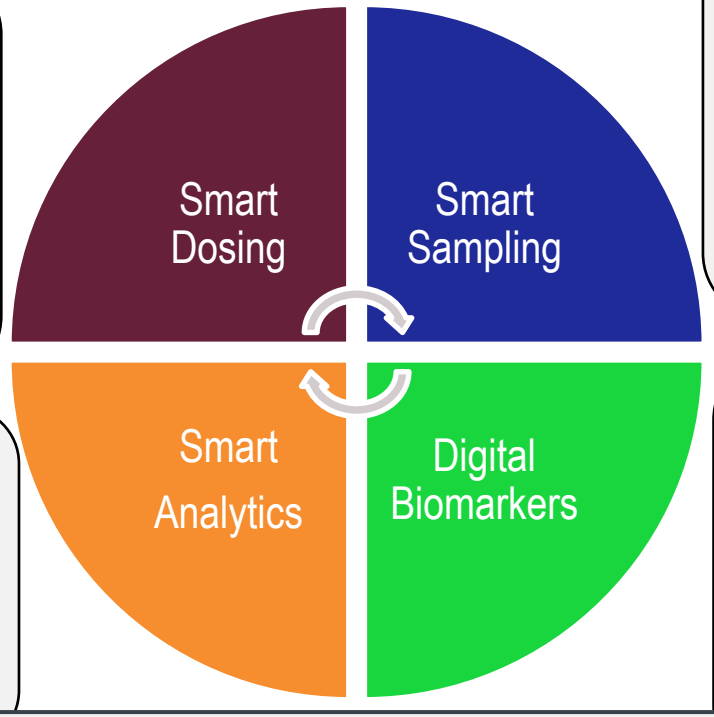
MSD

# Smart Trials: A Patient Centric Approach to Enriching Clinical Trial Data

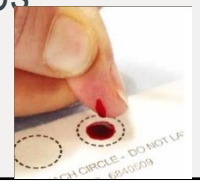
Smart Trials is a cross-functional, multi-year innovation project at Merck & Co., Inc. aimed at **enriching clinical trial datasets** and enabling more **rapid and informed clinical decisions** through a **patient-centric approach**

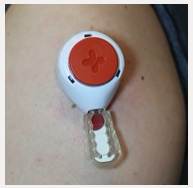
**Smart Dosing:** technologies to record and transmit dosing information (i.e. if and when the patient took the drug)



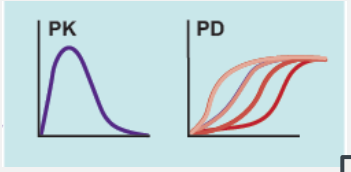




**Smart Sampling:** technologies for use in the outpatient setting to collect PK, PD, or biomarker samples coupled with date/time stamps





**Smart Analytics:** analytic platforms that can integrate and visualize data in real-time




**Digital Biomarkers:** objective measures collected using digital devices that reflect physiological responses to disease progression or therapeutic intervention


Clinic

**HIGH** Cost, Skill, Burden

**LOW** Cost, Skill, Burden

Patients

**Site Centric Approach:** *Bring the **patient** to the trial*

**Patient-Centric Approach:** *Bring the trial to the **patient***

Disclaimer: These are just a few examples of the technologies and not an endorsement of any product.

MSD

# Smart Sampling: What is it?

- Aim is to develop outpatient (at-home) collection of samples that can be used for measurement of drug and/or biomarkers
- Reduced patient burden compared to wet sampling (µL vs. mL quantities)
- Can be shipped using regular mail, does not require dry ice

- **Current approaches**
  - Fingerstick sampling, blood spotted on Dried Blood Spot card
  - Sample barcode pre-assigned to each subject/nominal time; scanned by subject with smart phone/e-diary upon collection and eDiary entry
  - Time/date recorded by subjects with eDiary
  - DBS cards returned to clinical site and shipped to BA lab for concentration analysis

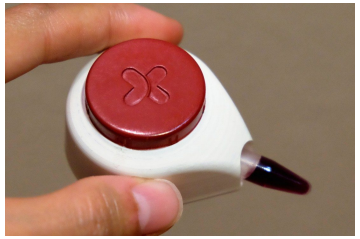
- **Future approaches**
  - Less painful methods of sampling
  - Collection on paper or polymer matrix
  - Automated date/time stamps
  - Sample barcode assigned at time of collection

DBS

eDiary

VAMS

TAP™



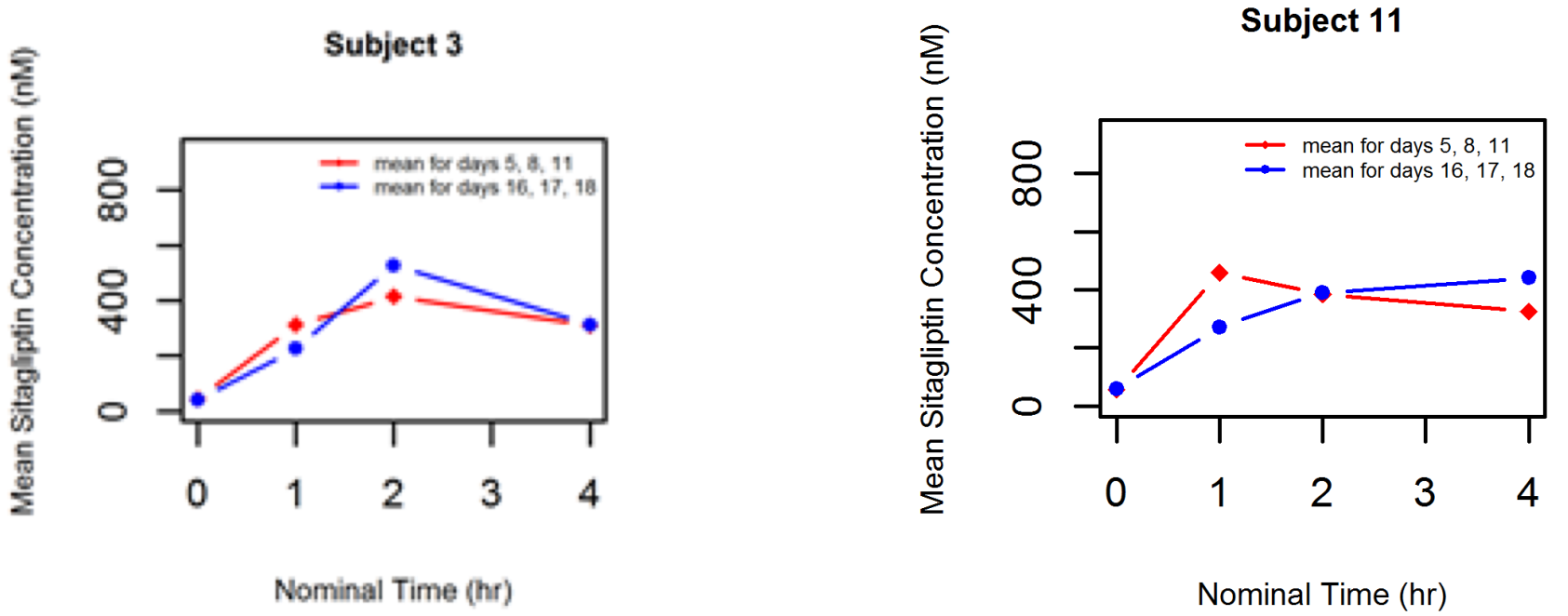
HemoLink

# Clinical Pilot Studies: Two pilot studies conducted, similar design but using different technologies of interest

- Study designs:
  - 2 period, fixed sequence studies
  - QD sitagliptin to 16 healthy subjects
  - Period 1 – “Smart” dosing & sampling (Days 1-14)
    - Dosing date/time captured via smart packaging (passively) and eDiary (patient-reported)
    - eDiary for date/time capture of PK samples
    - In-clinic and at-home PK sampling
    - DNA profiling of select PK samples for confirmation of patient ID
  - Period 2 – “Traditional” dosing & sampling (Days 15-16)
    - Traditional packaging
    - In-clinic PK sampling
- Questionnaire for subject feedback

# Smart Sampling Results from Pilot #1

Representative Individual PK Profiles: In-Clinic vs. At-Home Fingerstick DBS




**Red**: at-home samples collected using smart dosing & sampling methods (Mean of Days 5, 8, 11)
**Blue**: in-clinic samples collected using traditional methods (Mean of Days 16, 17, 18)

- Mean PK profiles were generally similar for at-home samples collected using smart dosing and sampling methods vs. in-clinic samples collected using traditional methods
- PK and associated variability from in-clinic vs. at-home samples were similar
- Several cases of missing or incorrect barcode scans using eDiary

# Fingerstick DBS sampling: PK and eDiary Data

## eDiary Web Portal

Study Overview

| Patient | Day 1-Clinic PreDose | Day 1 Clinic-1 Hour Sample | Day 2-Dose | Day 3-Dose | Day 4-Dose | Day 5-Sample+Dose | Day 5-8 Hour Sample | Day 6-Dose | Day 7-Dose | Day 8-Sample+Dose | Day 8-8 Hour Sample | Day 9-Dose | Day 10-Sample+Dose | Day 10-4 Hour Sample | Day 11-Dose | Day 12-Sample+Dose | Day 12-1 Hour Sample | Day 12-8 Hour Sample | Day 13-Dose | Day 14-Clinic PreDose | Day 14-8 Hour Sample | Training |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TOTAL | 16 | 16 | 16 | 16 | 16 | 15 | 15 | 16 | 16 | 15 | 14 | 16 | 15 | 15 | 16 | 15 | 15 | 15 | 16 | 16 | 15 | 6 |
| AVG | -0.6 | -0.1 | -0.5 | +0.1 | +0.1 | +0.2 | -0.2 | -3.7 | -2.6 | -0.1 | -0.2 | -2.1 | +0.1 | -0.7 | -1.6 | +0.2 | -0.2 | -0.4 | -1.5 | -1.7 | +0.0 | |
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AN 12 PK data indicate potential missed doses on 3 at-home study days; however, these doses were reported via eDiary and Smart Packaging

- DNA profiling confirmed patient ID
- **Potentially dispensed pill without ingestion**

| | Sitagliptin Concentration (ng/mL) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Ctrough | C8hr | Ctrough | C8hr | Ctrough | C4hr | Ctrough | C1hr | C8hr | Ctrough | C8hr |
| AN | Day 1, 0hr | Day 1, 1hr | Day 5, 0hr | Day 5, 8hr | Day 8, 0hr | Day 8, 8hr | Day 10, 0hr | Day 10, 4hr | Day 12, 0hr | Day 12, 1hr | Day 12, 8hr | Day 14, 0hr | Day 14, 8hr |
| 1 | BLQ | 335 | 19 | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ | 31 | 119 |
| 2 | BLQ | 226 | 65 | 138 | 34 | 100 | 41 | 315 | 30 | 359 | 133 | 34 | 173 |
| 3 | BLQ | 161 | 37 | 172 | 36 | 151 | 60 | 420 | 47 | 326 | 103 | 36 | 231 |
| 4 | BLQ | 235 | 34 | 151 | 31 | 151 | 42 | 268 | 33 | 850 | 132 | 14 | 92 |
| 5 | BLQ | 449 | 25 | 133 | 24 | 157 | 27 | 366 | 32 | 835 | 141 | 106 | 196 |
| 6 | BLQ | 281 | 36 | 163 | 45 | 172 | 23 | 275 | 34 | 284 | 176 | 31 | 134 |
| 7 | BLQ | 143 | 42 | 215 | 42 | 172 | 38 | 312 | 49 | 511 | 151 | 44 | 183 |
| 8 | BLQ | 357 | 29 | 148 | 25 | 144 | 19 | 257 | 34 | 31 | 170 | 26 | 129 |
| 9 | BLQ | 373 | 27 | 124 | 29 | 188 | 26 | 308 | 33 | 257 | 108 | 43 | 151 |
| 10 | BLQ | 438 | 33 | 74 | 26 | 82 | 39 | 79 | 44 | 101 | 84 | 19 | 86 |
| 11 | BLQ | 416 | 28 | 132 | 26 | 115 | 27 | 157 | 31 | 516 | 125 | BLQ | 144 |
| 12 | BLQ | 315 | BLQ | 66 | BLQ | 65 | BLQ | 140 | 22 | 100 | 165 | 20 | 91 |
| 13 | BLQ | 327 | 40 | 176 | 38 | 181 | 42 | 279 | 45 | 579 | 132 | 35 | 161 |
| 14 | BLQ | 451 | 47 | 28 | 33 | 137 | 59 | 348 | 52 | 448 | 153 | 41 | 170 |
| 15 | BLQ | 411 | 28 | 155 | 30 | missing | 24 | 133 | 26 | 423 | 286 | 29 | 172 |
| 16 | BLQ | 164 | 79 | 273 | 80 | 229 | 58 | 53 | 89 | 78 | 308 | 78 | 224 |

BLQ = below the limit of quantification (5 ng/mL)

**Key Take-Aways**

Data suggest need for dosing confirmation in some cases (e.g. ingestible sensors or visual dosing confirmation)

# Fingerstick DBS sampling: PK and eDiary Data

## eDiary Web Portal

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| 0013 | 01-OCT-2016 | 01-OCT-2016 | 02-OCT-2016 | 03-OCT-2016 | 04-OCT-2016 | 05-OCT-2016 | 05-OCT-2016 | 06-OCT-2016 | 07-OCT-2016 | 08-OCT-2016 | 08-OCT-2016 | 09-OCT-2016 | 10-OCT-2016 | 10-OCT-2016 | 11-OCT-2016 | 12-OCT-2016 | 12-OCT-2016 | 12-OCT-2016 | 13-OCT-2016 | 14-OCT-2016 | 14-OCT-2016 | 0 |
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| 0015 | 01-OCT-2016 | 01-OCT-2016 | 02-OCT-2016 | 03-OCT-2016 | 04-OCT-2016 | 05-OCT-2016 | 05-OCT-2016 | 06-OCT-2016 | 07-OCT-2016 | 08-OCT-2016 | | 09-OCT-2016 | 10-OCT-2016 | 10-OCT-2016 | 11-OCT-2016 | 12-OCT-2016 | 12-OCT-2016 | 12-OCT-2016 | 13-OCT-2016 | 14-OCT-2016 | | 0 |
| 0016 | 01-OCT-2016 | 01-OCT-2016 | 02-OCT-2016 | 03-OCT-2016 | 04-OCT-2016 | 05-OCT-2016 | 05-OCT-2016 | 06-OCT-2016 | 07-OCT-2016 | 08-OCT-2016 | 08-OCT-2016 | 09-OCT-2016 | 10-OCT-2016 | | 11-OCT-2016 | | | | 13-OCT-2016 | | | |

AN 1 PK data indicate several potential missed doses; however, these doses were reported via eDiary and Smart Packaging

- **DNA profiling indicates this subject had someone else collect most of the at-home samples**

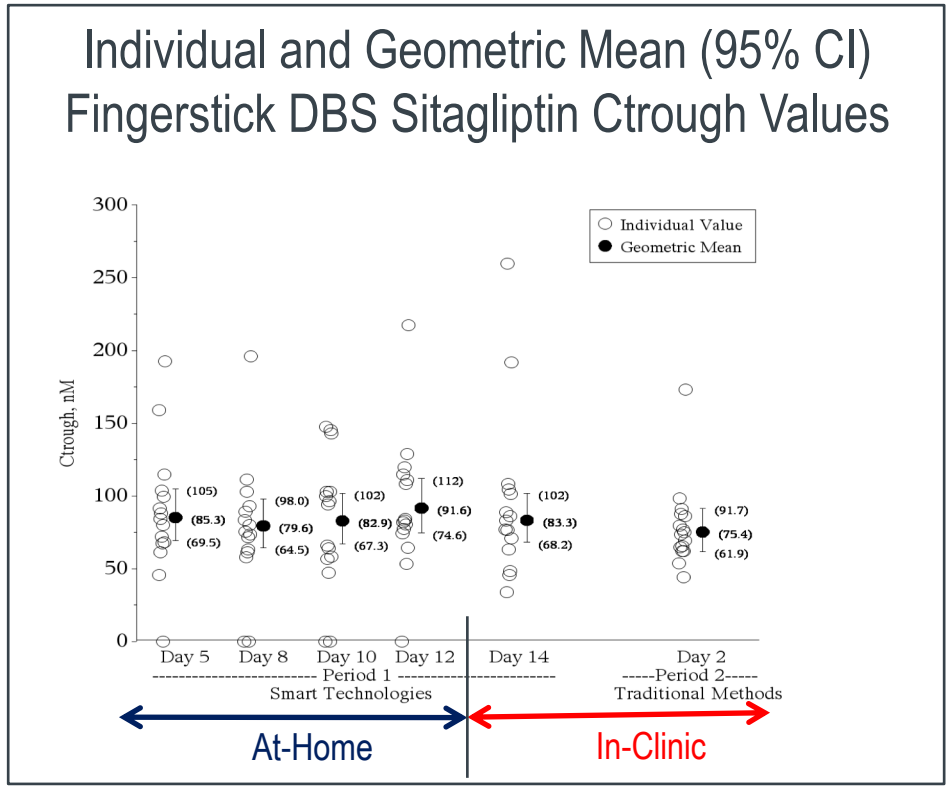
| | Sitagliptin Concentration (ng/mL) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Ctrough | C8hr | Ctrough | C8hr | Ctrough | C4hr | Ctrough | C1hr | C8hr | Ctrough | C8hr |
| AN | Day 1, 0hr | Day 1, 1hr | Day 5, 0hr | Day 5, 8hr | Day 8, 0hr | Day 8, 8hr | Day 10, 0hr | Day 10, 4hr | Day 12, 0hr | Day 12, 1hr | Day 12, 8hr | Day 14, 0hr | Day 14, 8hr |
| 1 | BLQ | 335 | 19 | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ | BLQ | 31 | 119 |
| 2 | BLQ | 226 | 65 | 138 | 34 | 100 | 41 | 315 | 30 | 359 | 133 | 34 | 173 |
| 3 | BLQ | 161 | 37 | 172 | 36 | 151 | 60 | 420 | 47 | 326 | 103 | 36 | 231 |
| 4 | BLQ | 235 | 34 | 151 | 31 | 151 | 42 | 268 | 33 | 850 | 132 | 14 | 92 |
| 5 | BLQ | 449 | 25 | 133 | 24 | 157 | 27 | 366 | 32 | 835 | 141 | 106 | 196 |
| 6 | BLQ | 281 | 36 | 163 | 45 | 172 | 23 | 275 | 34 | 284 | 176 | 31 | 134 |
| 7 | BLQ | 143 | 42 | 215 | 42 | 172 | 38 | 312 | 49 | 511 | 151 | 44 | 183 |
| 8 | BLQ | 357 | 29 | 148 | 25 | 144 | 19 | 257 | 34 | 31 | 170 | 26 | 129 |
| 9 | BLQ | 373 | 27 | 124 | 29 | 188 | 26 | 308 | 33 | 257 | 108 | 43 | 151 |
| 10 | BLQ | 438 | 33 | 74 | 26 | 82 | 39 | 79 | 44 | 101 | 84 | 19 | 86 |
| 11 | BLQ | 416 | 28 | 132 | 26 | 115 | 27 | 157 | 31 | 516 | 125 | BLQ | 144 |
| 12 | BLQ | 315 | BLQ | 66 | BLQ | 65 | BLQ | 140 | 22 | 100 | 165 | 20 | 91 |
| 13 | BLQ | 327 | 40 | 176 | 38 | 181 | 42 | 279 | 45 | 579 | 132 | 35 | 161 |
| 14 | BLQ | 451 | 47 | 28 | 33 | 137 | 59 | 348 | 52 | 448 | 153 | 41 | 170 |
| 15 | BLQ | 411 | 28 | 155 | 30 | missing | 24 | 133 | 26 | 423 | 286 | 29 | 172 |
| 16 | BLQ | 164 | 79 | 273 | 80 | 229 | 58 | 53 | 89 | 78 | 308 | 78 | 224 |

BLQ = below the limit of quantification (5 ng/mL)

## Key Take-Aways

Confirmation of patient ID (via DNA profiling or other means) for at-home samples is useful

# Smart Sampling Results from Pilot #2

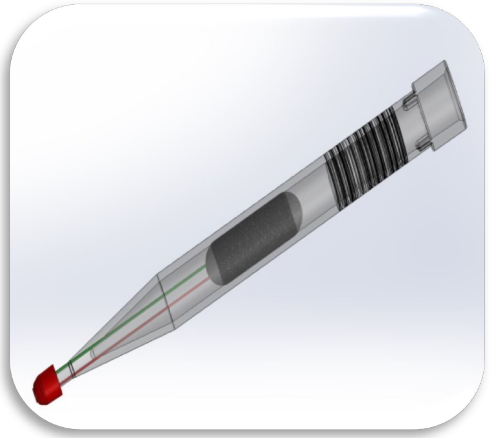



- **eDiary data:** Two subjects had missing eDiary entries for collected PK samples
- **Comparison of PK & Dosing Data:** Undetectable sitagliptin concentrations for at-home samples collected from 2 subjects, despite reported dosing via Smart Packaging & eDiary
  - In one case, DNA profiling confirmed subject ID → potentially dispensed dose without ingestion
  - In another case, DNA profiling did not confirm subject ID → suggests samples collected by someone else

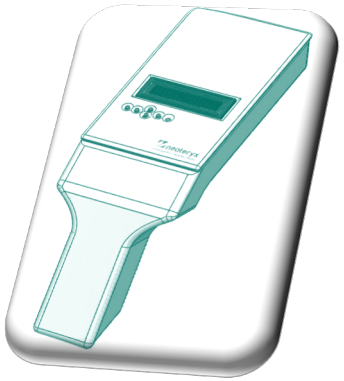
- Sitagliptin concentrations from samples collected at-home were generally similar to those collected in-clinic
- Missing eDiary data highlight importance of adding automated date/time stamps
- Smart Packaging is an improved yet imperfect indicator of adherence
- DNA profiling can be a useful tool as a means of confirming patient ID and sample disambiguation

# Time Stamper Concept from Neoteryx

## Captures the exact time the sample is taken



- Sampling event triggers clock
- Real-time tracking
- RFID chip in sampler body
- RFID chip scanner

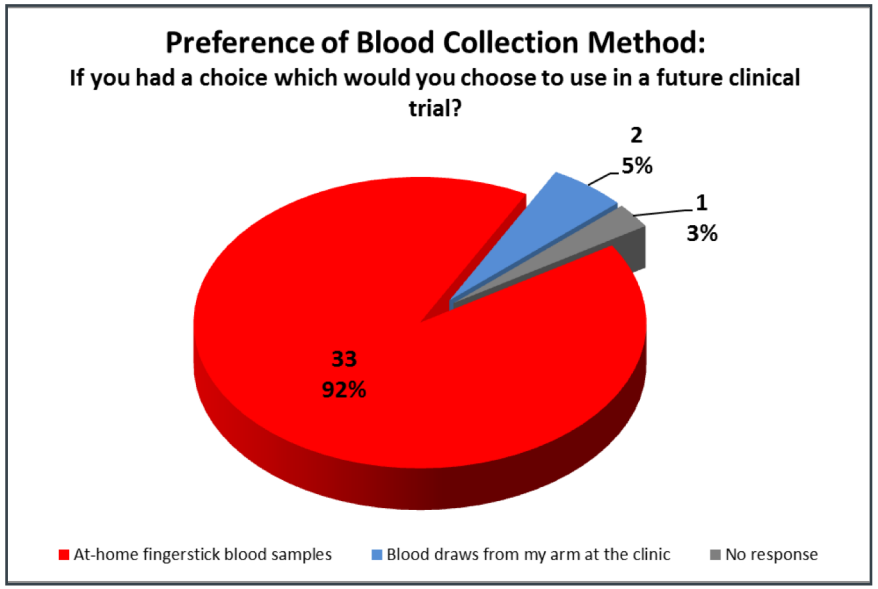


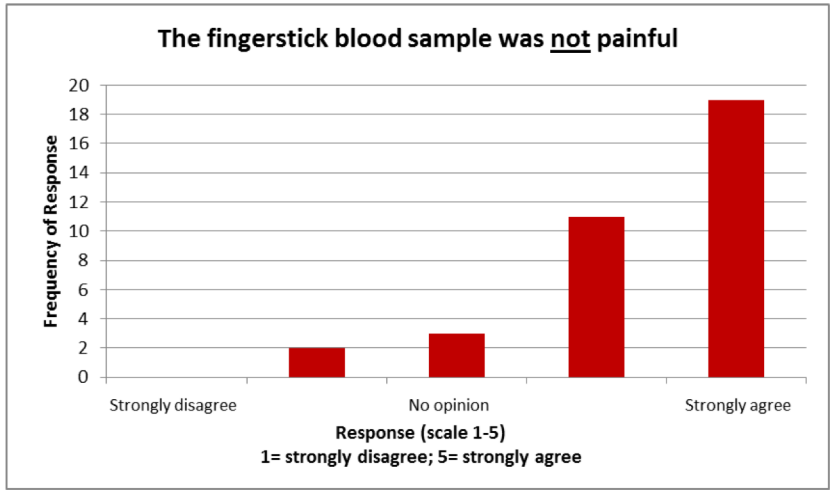
# Rendering of Potential Commercial Product

# Prototype Demonstration

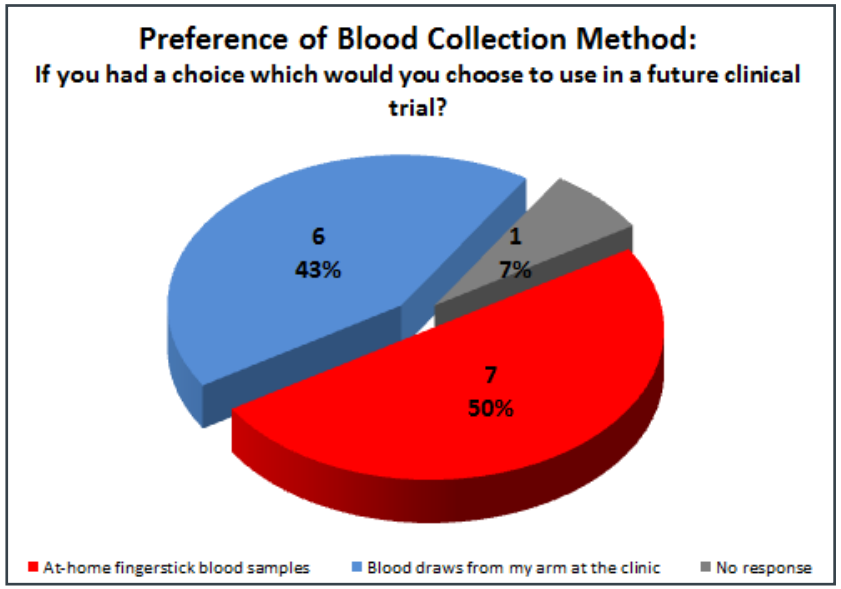
# Smart Sampling: Questionnaire Results

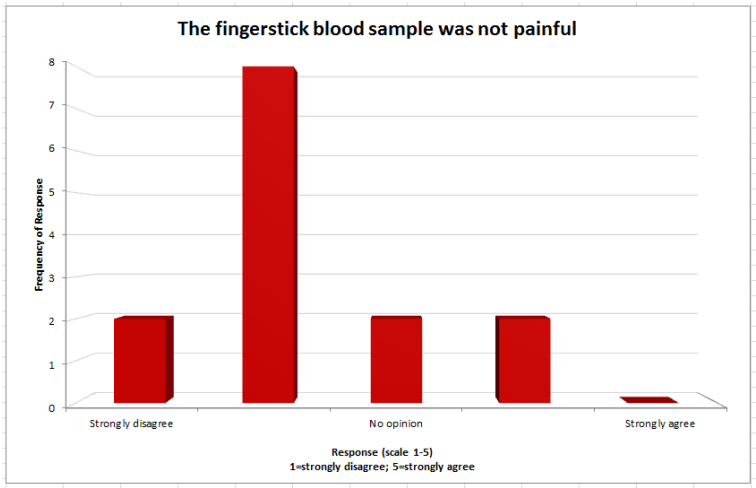
## **MK-X Study** (1 sample/day, n=36)




## **Smart Trials Pilot #1** (4 samples/day, n=14)



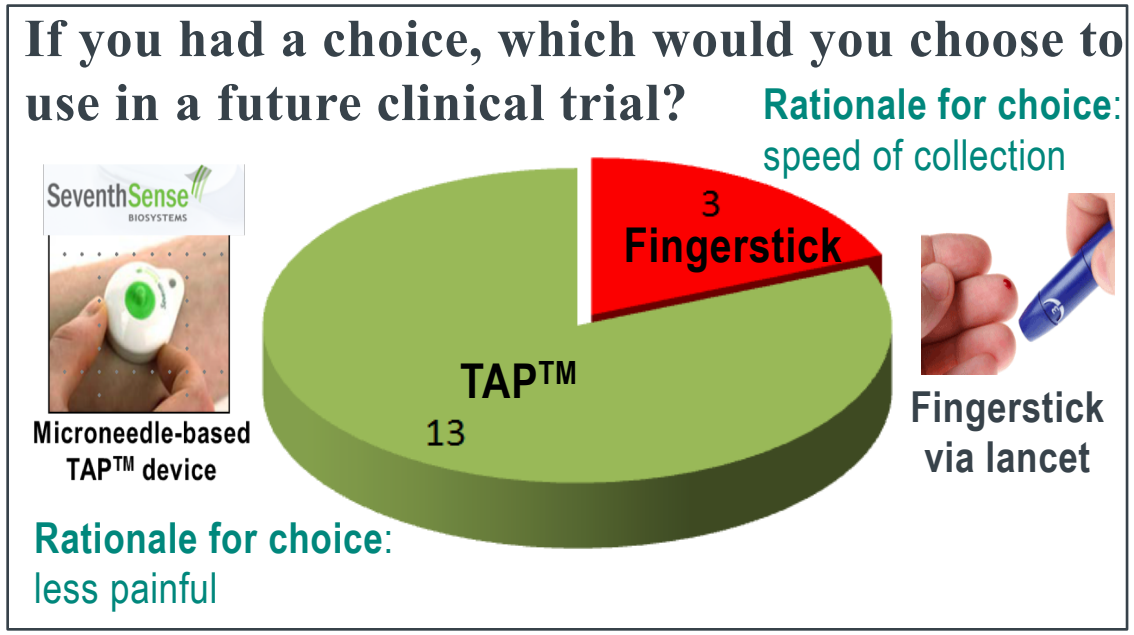



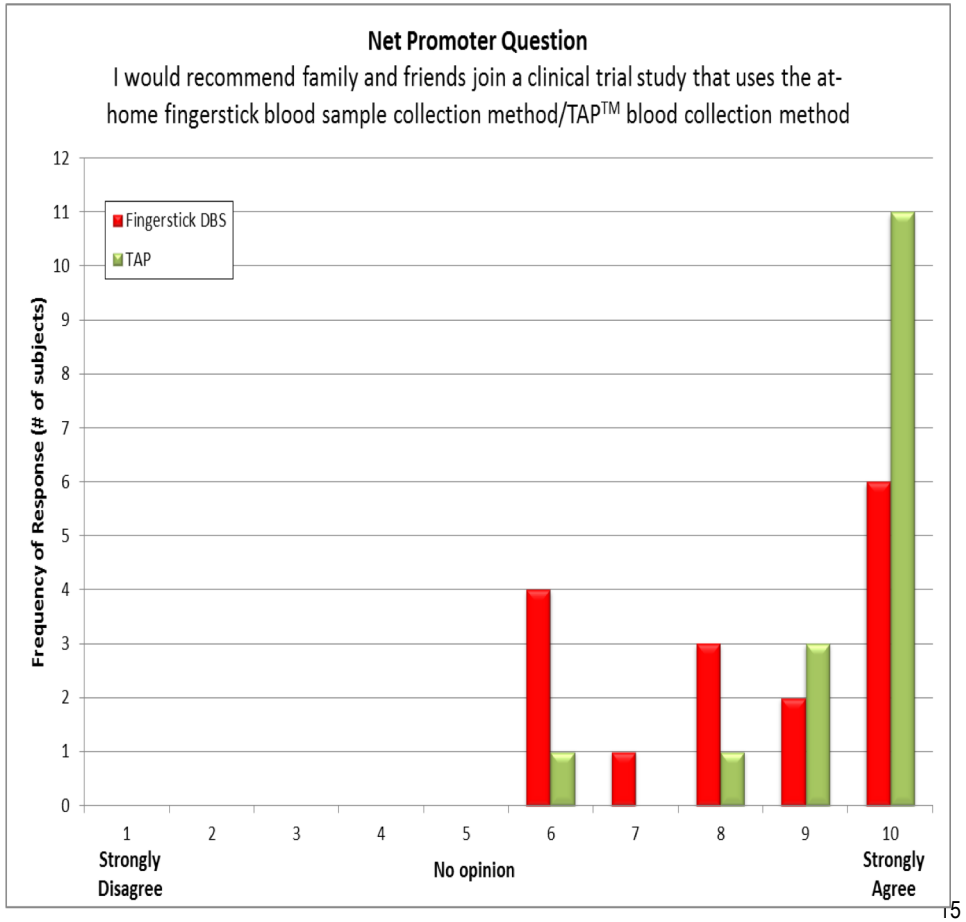

**Reduced frequency of fingerstick sampling may result in less pain and help drive subject preference toward at home fingerstick sampling**

# Smart Sampling: Questionnaire Results

## TAP™ device

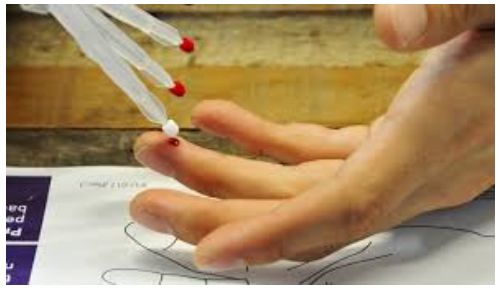
- Minimally invasive, micro-needle based sampling via push-button
- Painless, no sharp exposure
- This trial used TAP™ for limited in-clinic sampling (performed by clinic staff) to get subject feedback



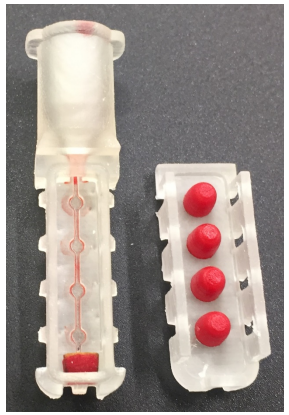

**Less painful methods of sampling may be beneficial in driving subject preference for at-home sampling**

# Smart Sampling Pilot #3: Fingerstick, Venous, Hemolink



**Fingerstick via lancet**

**Venous**



**Tasso Hemolink with Mitra**

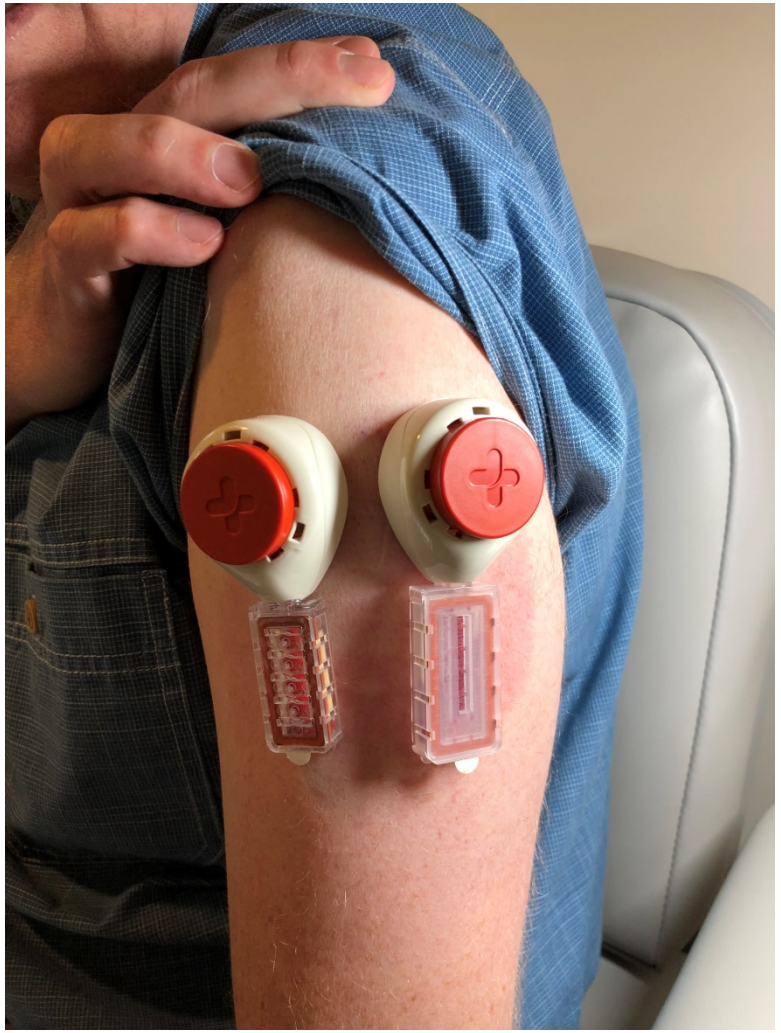
## Part 1

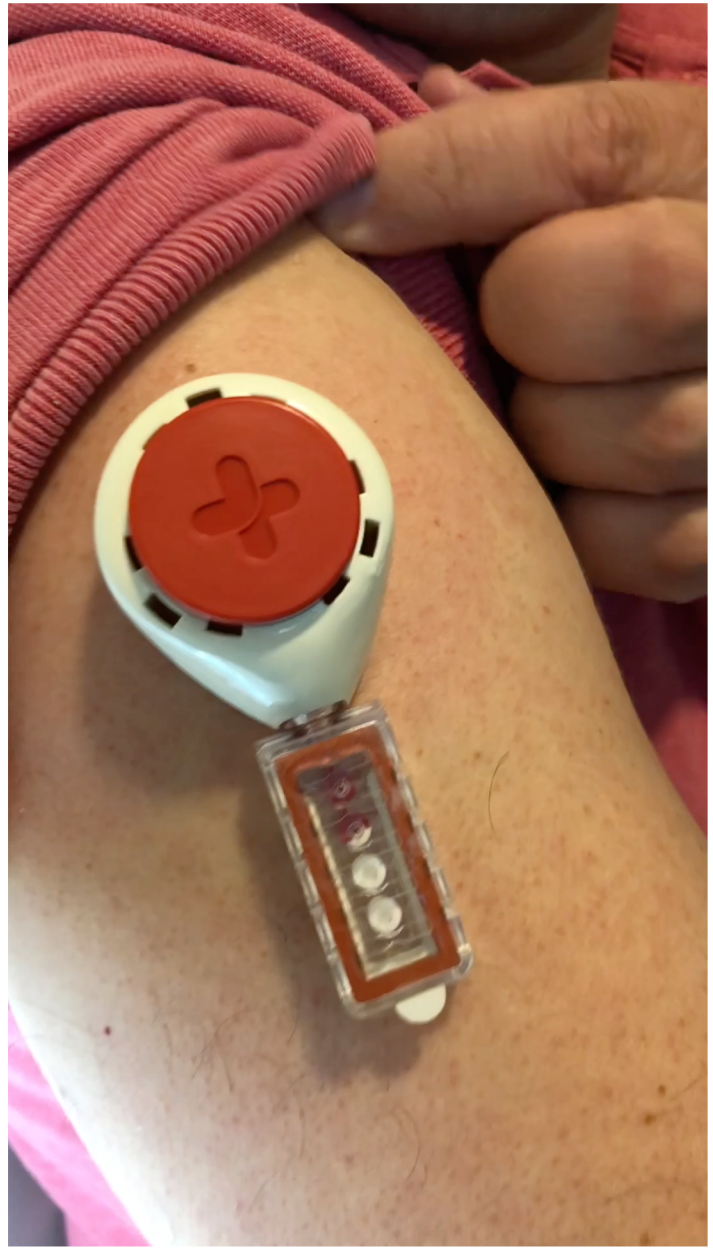
- Dose acetaminophen and caffeine
- VAMS sampling by Hemolink in clinic
- 4 subjects, Time points Predose, 0.5, 1, 3, 6 hour
- Profiles of acetaminophen and caffeine

## Part 2

- Dose acetaminophen and caffeine
- VAMS sampling by Hemolink, Venous, Finger stick in clinic
- 32 subjects, Time points 1 and 2 hour post dose
- Comparisons of sampling performance

MSD

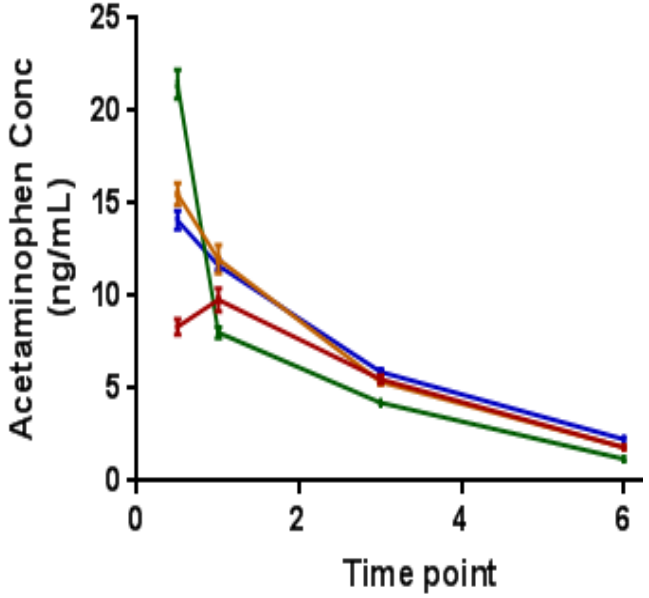


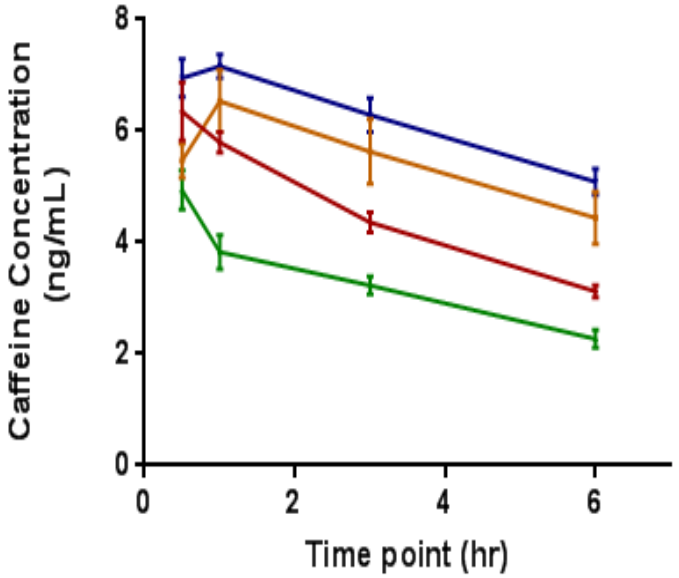


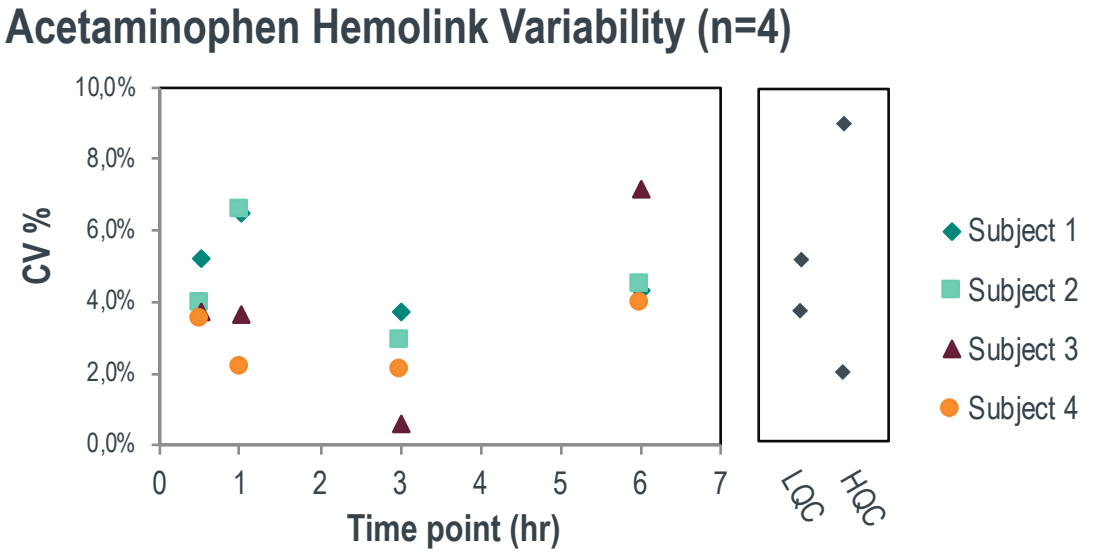
# Smart Sampling Pilot #3: Hemolink

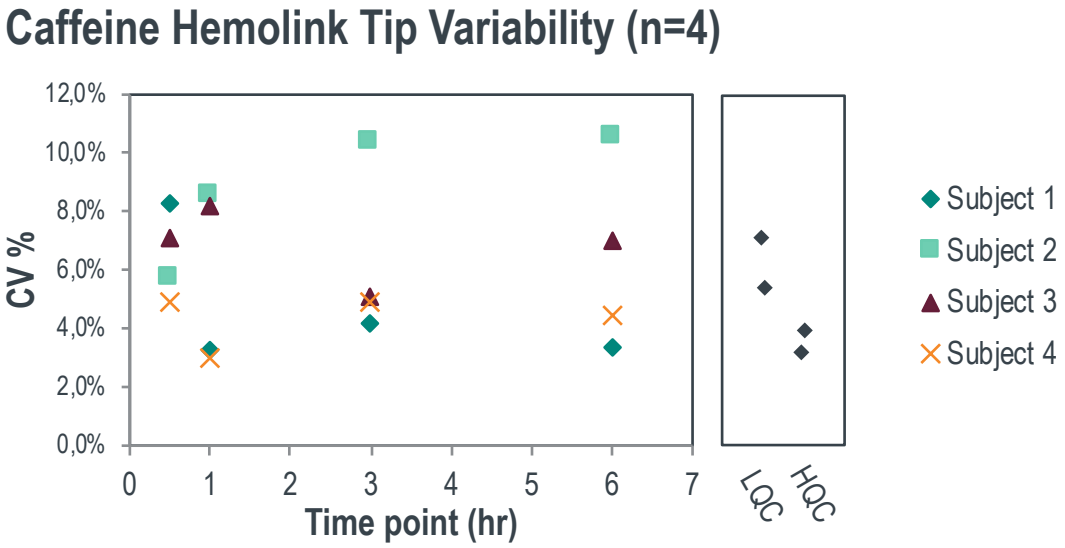
## Part 1

- Hemolink+VAMS in clinic
- Profiles of acetaminophen and caffeine
- CV% for tip 1-4 are <11% and are consistent with QC performance for both analytes



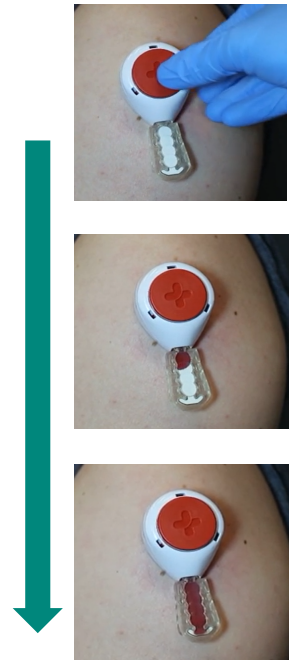
# Smart Sampling Pilot #3: Hemolink

## Part 1

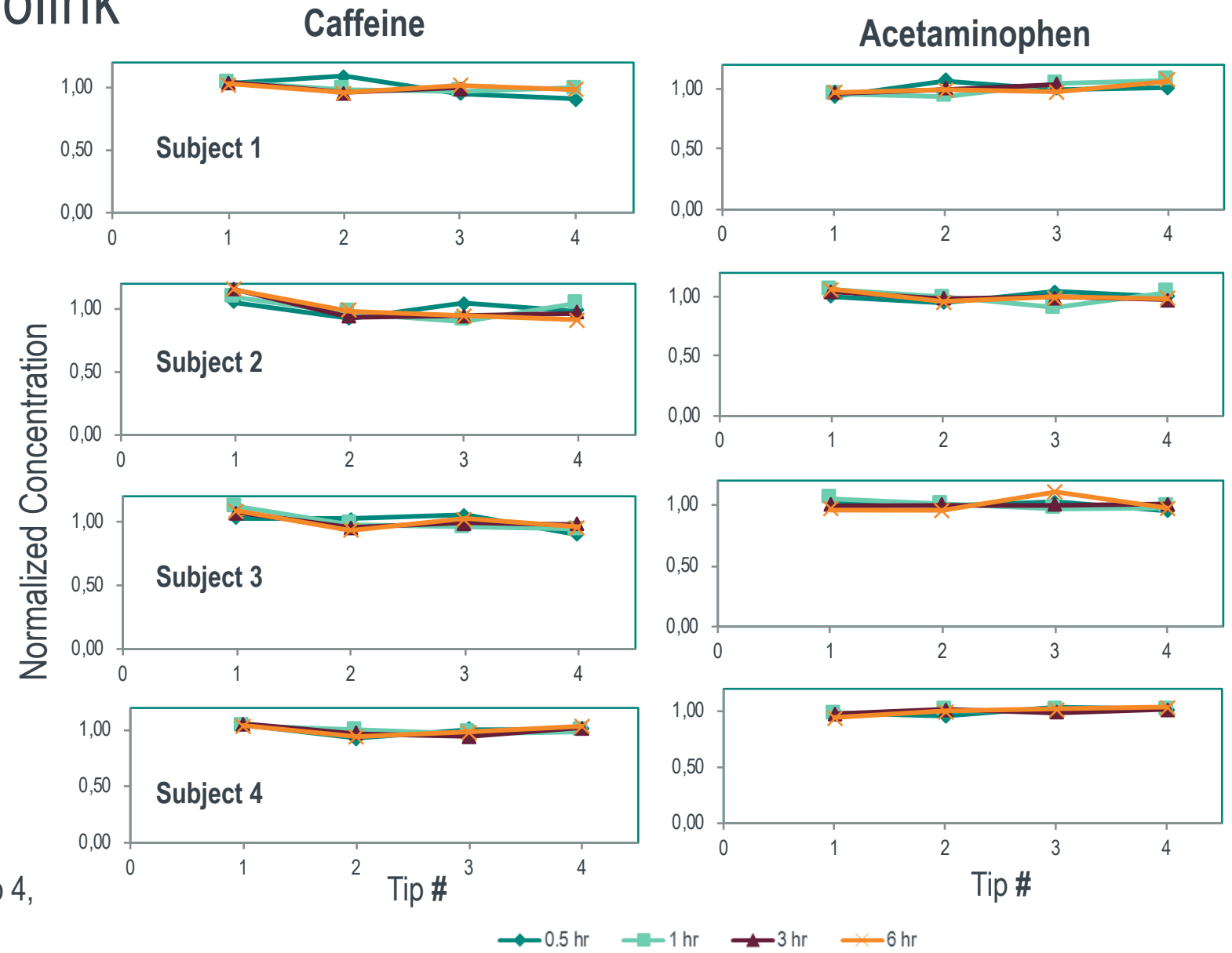
- Hemolink+VAMS in clinic
- No trends between tip 1 and tip 4 were observed

**Key Take-Aways**

Caffeine and Acetaminophen can be reliably detected with the Tasso device. Variability between tips across the device is acceptable.



Blood flows from tip 1 to tip 4, can this impact sample volume due to over-sampling or under-sampling

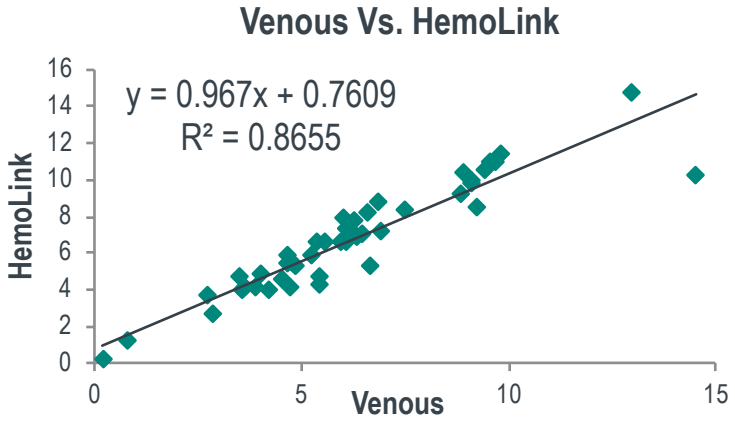


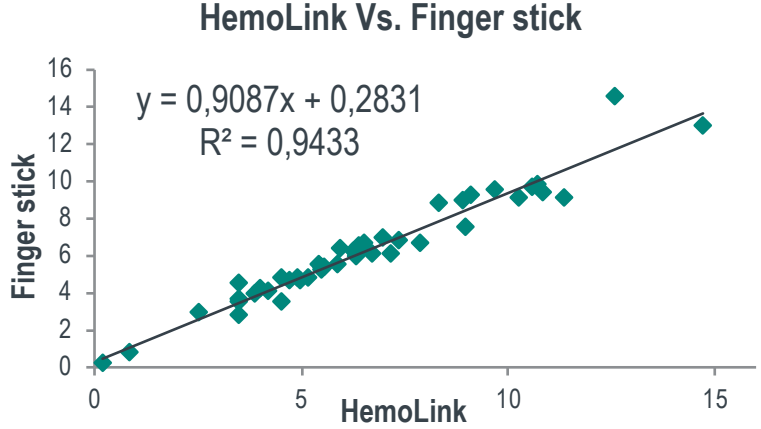
# Smart Sampling Pilot #3: Fingerstick, Venous, Hemolink

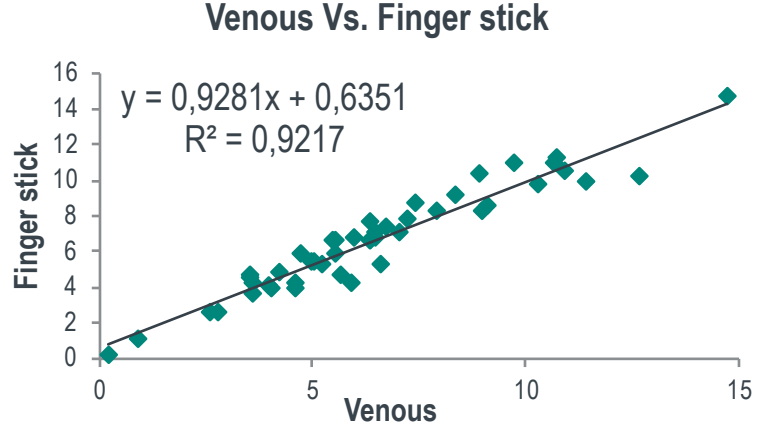
## Part 2

- Hemolink, Venous, Fingerstick VAMS in clinic-Sampling Performance
- Two time points for acetaminophen and caffeine

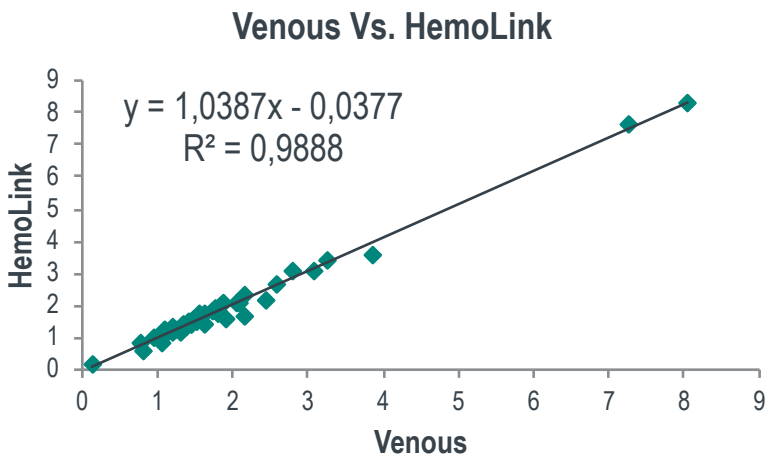
## Acetominophen

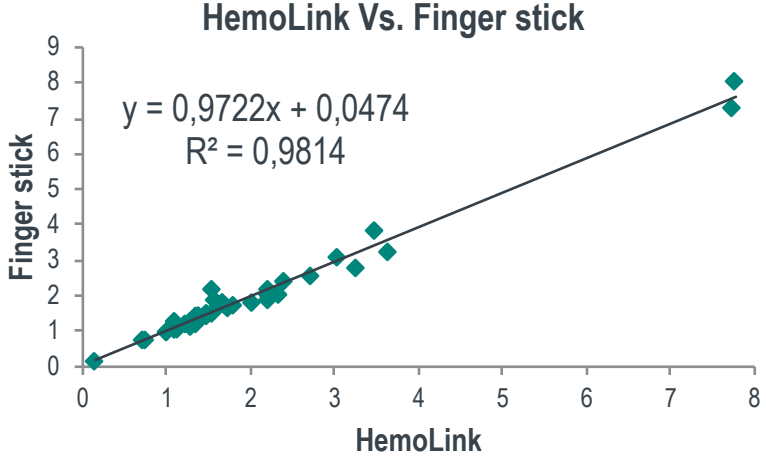


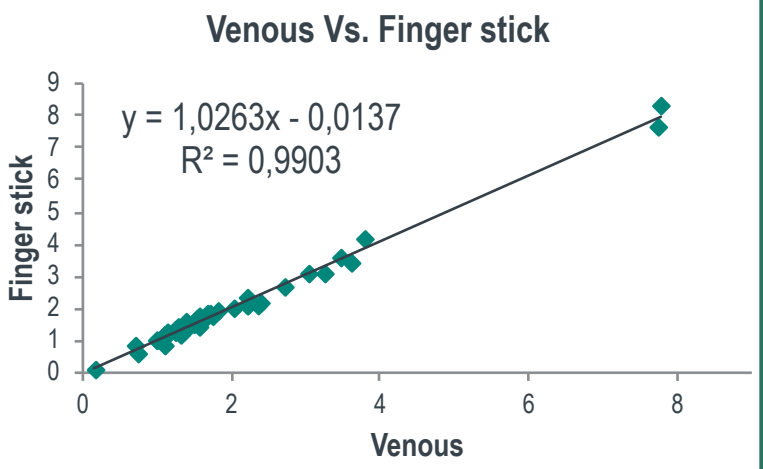



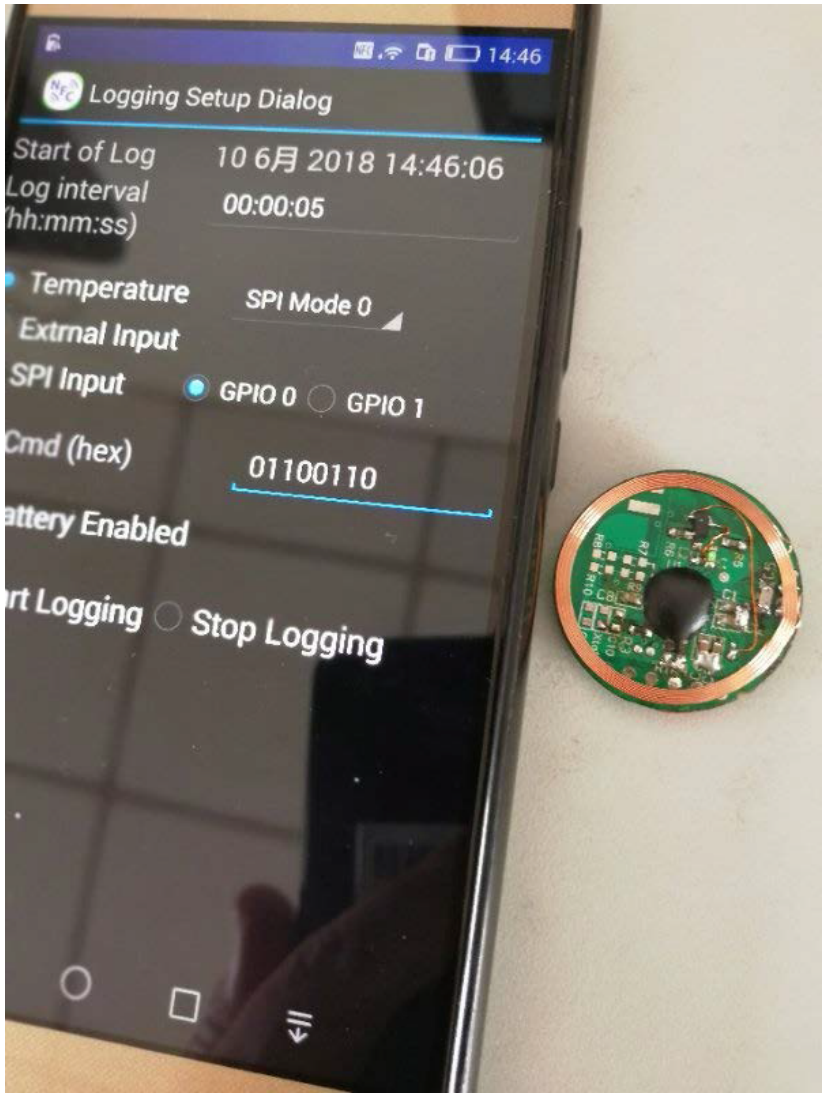

## Caffeine



# Date and Time Collection


- Records time and temperature every 10 min for 2 weeks
- Starts when button is pressed
- Wireless communication with smartphone or smartbox (to be design in partnership with Merck)

# Smart Sampling Challenges

## Logistical

- Clinical site and Patient training – this can involve several clinical site all over the world and language translation
- Patient compliance and sample collection reliability, at home sampling needs to be a simple and straightforward as possible
- Regulatory – how are devices treated and what regulatory approval is needed in each country
- Time stamp-how do we reliably collect a time stamp and how will the data flow.
- Supply – scaling up manufacturing for device availability, lot-to-lot variability

## Bioanalytical Sample Analysis

- Sensitivity – low sample volume
- Stability in the dried state – this is a bigger concern in later trials when samples may ship from multiple clinical sites and storage may occur for longer at central laboratories
- Extractability of aged or stressed dried samples
- Automation
- Tedious sample handling and storage

# Conclusions and Future Directions

- Smart Trials initiative is aimed at modernizing clinical trials in order to:
  - improve data quality
  - enrich data sets
  - drive a more patient-centric approach
- Pilot study results demonstrate feasibility and subject acceptance of “smart” approaches for future use and have helped identify areas of focus for further investigations:
  - automated date/time stamps for sampling, painless methods of sampling, more streamlined data integration
- Future directions:
  - Continue evaluating digital health technologies & outpatient sampling approaches in pilot trials to enable readiness for implementation in clinical development programs
  - Inclusion of Smart Trials approaches into clinical development programs

# Acknowledgements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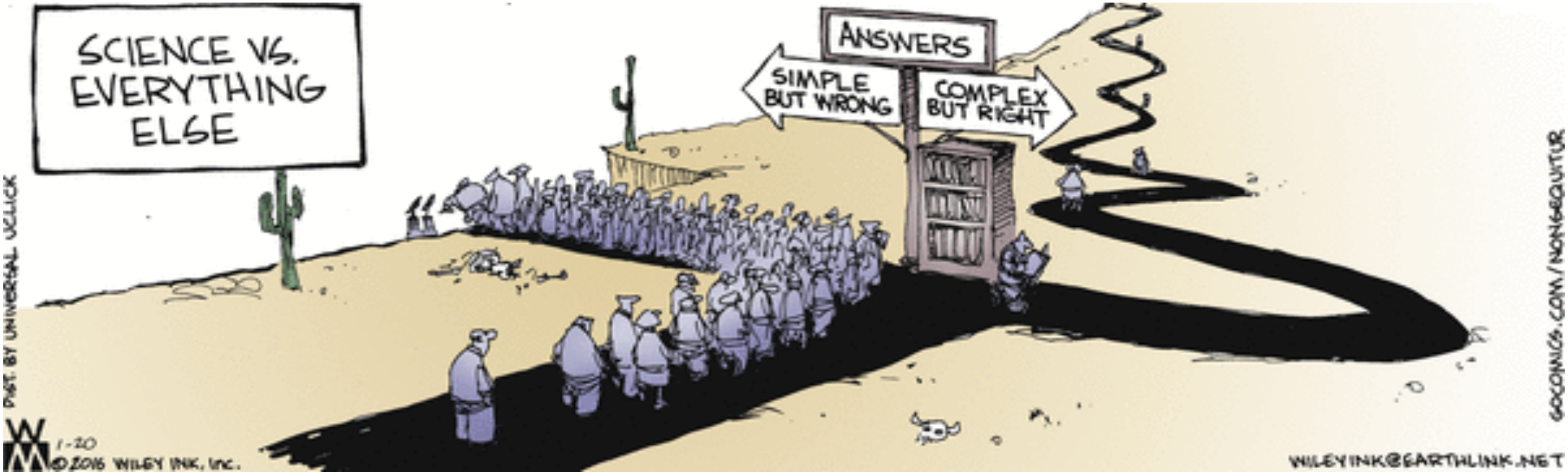
- Gowri Murthy
- Rubi Burlage
- Andra Goldman
- Jeff Sachs
- Kai Bode
- Stephany Contrella
- Tian Zhao

…and *many others* on the Smart Trials team


# Questions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