21st Annual Symposium
Clinical & Pharmaceutical Solutions through Analysis

United to Beat Disease: Partners in Healthcare, Partners in Science, Partners in Technology & Innovation

2018 Program Chair
Alla Kloss
Sanofi

Microsampling & Patient Centric Sampling

A journey through what it is and how you can incorporate it into your workflows

Monday 15th October 2018, 12:00-16:00 University Grille

Short Course Outline

12:00 Welcome & Introductions
Neil Spooner & Joe Siple

12:15 Introduction to Microsampling
Presentation - Neil Spooner

13:00 Practical Considerations for the Implementation of Microsampling
Discussion - Melanie Anderson

13:30 Break

13:45 Practical Considerations for the Development & Qualification / Validation of Bioanalytical Methods
Discussion - Tim Olah & Enaksha Wickremsinhe

14:30 Practical Considerations for the Use of Microsampling in Clinical Studies
Discussion - Kevin Bateman, Tim Olah, Enaksha Wickremsinhe & Neil Spooner

15:15 Emerging Microsampling Technologies
Presentation - Kevin Bateman

15:45 Summary & Wrap-up
Joe Siple

16:00 End

Instructors

- Melanie Anderson – Merck
- Kevin Bateman – Merck
- Tim Olah – Bristol-Myers Squibb
- Joe Siple – New Objective
- Neil Spooner – Spooner Bioanalytical Solutions
- Enaksha Wickremsinhe – Eli Lilly & Co

Introduction to Microsampling

Neil Spooner Ph.D., C.Chem., FRSC (*neil@spoonerbioanalytical.co.uk*)

Founder & Director - Spooner Bioanalytical Solutions Ltd, UK

Senior Visiting Research Fellow - School of Life & Medical Sciences, University of Hertfordshire, UK

Senior Editor – Bioanalysis Journal

What is microsampling?

Conventional Volumes
(200 µL – ? mL)

Micro-volumes
(≤ 100 µL)

Technologies for collecting and analysing smaller blood and plasma / serum volumes for the accurate determination of circulating concentrations of therapeutic drugs, metabolites and biomarkers in pre-clinical and clinical studies

What are the drivers for implementation of microsampling?

Pre-clinical

- Ethical - 3Rs
  - Reduction in rodent animal number requirements
    - Elimination of TK satellites reduces number of animals by 30-40%
      - Effects primarily on reticulocytes; no affect in overt toxicity assessment, e.g., hepatotoxicity, renal toxicity*
    - Serial TK & PK sampling in mice
    - Discovery PK, mouse TK & PK & juvenile studies
  - Refinement of bleeding technique
    - Reduction, or elimination of rodent warming
    - Sampling from more convenient / less disruptive location

*Powles-Glover *et al* (2014) *Reg. Toxicol. Pharmacol*. **68**, 325-331

What are the drivers for implementation of microsampling?

Pre-clinical Continued

- Improved data quality
  - Exposure data in main study animals, rather than additional satellites
  - Direct correlation of exposure with PD and toxicological outcomes
- Enables samples to be taken for other purposes
  - Additional PK/TK timepoints, biomarkers, metabolites, Clin. Path. determinations, etc.
- Cost
  - Reduced animal numbers, housing, drug substance
    - …..but, consumable costs are higher

However…… May be an issue for metabolites in safety testing!

What are the drivers for implementation of microsampling?

Clinical

- Potential for simplified sample collection – 'finger prick' approach
- Ability to generate exposure data where otherwise difficult
  - This is about more than standard PK sampling for current clinical trial designs
  - Richer data sets
- Sampling in the home / pharmacy / local Doctor's
  - Self sampling / assisted sampling
- Obtain 'new' information
  - Demonstration of patient compliance
  - Therapeutic drug monitoring – correct dose, correct drug
  - Obtaining data during a clinical episode
- Facilitating pediatric studies
- Sampling in geographically remote locations
- Sampling critically ill patients

Facilitating patient driven healthcare……

What are the drivers for implementation of microsampling?

Clinical Continued

- Enables samples to be taken for other purposes
  - Biomarkers, metabonomics, co-medications
- Simplified workflows for dried blood approaches
  - No centrifugation, matrix transfer, aliquotting, etc. Facilitates automation
- Cost Savings
  - Particularly for dried samples – Ambient temperature shipment and storage where analyte stability is demonstrated

DBS sampling – Potential for cost savings…….

Removal of the need for dry ice shipments and frozen storage of samples represents considerable savings

- ~$40K for 1500 sample, multi-centre trial
  - See Neoteryx Clinical Trial Cost Calculator tool - http://calculator.neoteryx.com/

~30% of the dry ice shipments reported to have issues such as incorrect packaging or incorrectly completed documentation

- van Amsterdam & Waldrop (2010*) Bioanalysis* **2(11)** 1783-1786

Home Sampling – Potential for Cost Savings

Obtained by removing the requirement for subjects to travel to a central clinic on study days where only PK samples are being collected

	Phase II	Phase III
Cost Saving	**€93K**	**€310K**

Data is for an 'average' study defined as follows

- Average number of patients = 300 for Phase II, 1000 for Phase III
- Average number of sampling occasions per study where dosing is not occurring, or blood samples are not being collected for another purpose = 2
- Average subject expenses cost per visit to the clinic = £120

The following are not included in the cost savings

- 2-4 hours of subject time per visit
- Cost of the home sampling kit
- Subject training
- Staff costs associated with collection of these samples at the clinic

Cost savings for TDM of renal transplant & hemato-oncology pediatric patients

Total societal savings

- 43% for hemato-oncology (€277 to €158 per blood draw)
- 61% for nephrology(€259 to €102 per blood draw)
  - Includes healthcare costs provision, patient related costs & costs related to loss of productivity of the caregiver

Healthcare only savings

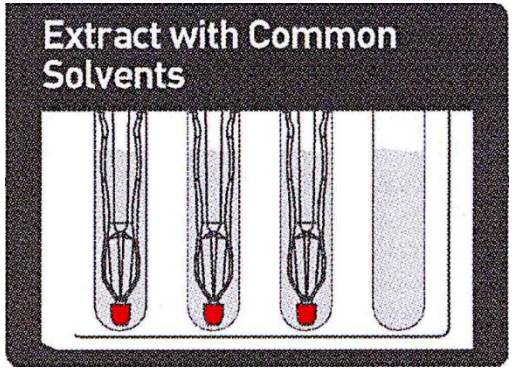
- 7% for hemato-oncology
- 21% for nephrology

Martial *et al* (2016) *PLOS ONE* | DOI:10.1371/journal.pone.0167433

Drivers for Implementation of Microsampling

Bioanalysis

- Potential for increased automation of sample extraction……..



- Increased communication with sample originators, and those responsible for data processing & submission
- Increased consideration of the journey of the sample
- Staff involvement with new technology development & implementation

Technologies – Dried Blood Spots

Established for neonatal screening for 50+ years

Delivers all the advantages of microsampling

PLUS - Simpler process

- Removes need for centrifugation or sub-aliquots
- Dry ice and freezers not required
  - BIG cost savings on sample shipments

Barfield *et al* (2008) *J. Chrom. B* **870**, 32-37; Spooner *et al* (2009) *Anal. Chem.* **81**, 1557-1563; Spooner *et al* (2010) *Bioanalysis* **2(8)**, 1515-1522; Pandya *et al* (2011) *Bioanalysis* **3(7)**, 779-786; Stokes *et al* (2011) *Lab. Animals* **45**, 109-113;

Automated analysis of DBS samples

ThermoFisher SCIENTIFIC

prolab Instruments GmbH

BSD ROBOTICS

Hudson ROBOTICS, INC.

CAMAG

Advion

Spark HOLLAND

PerkinElmer For the Better

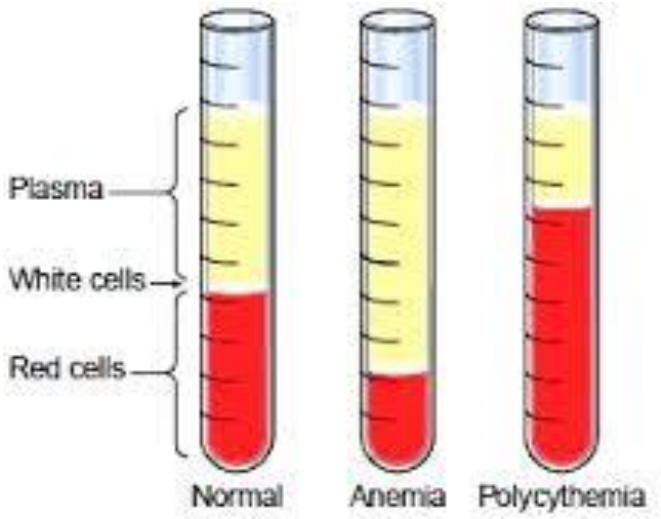
However…….

…..for quantitative analyses, an accurate volume needs to be spotted,

or punched from the sample

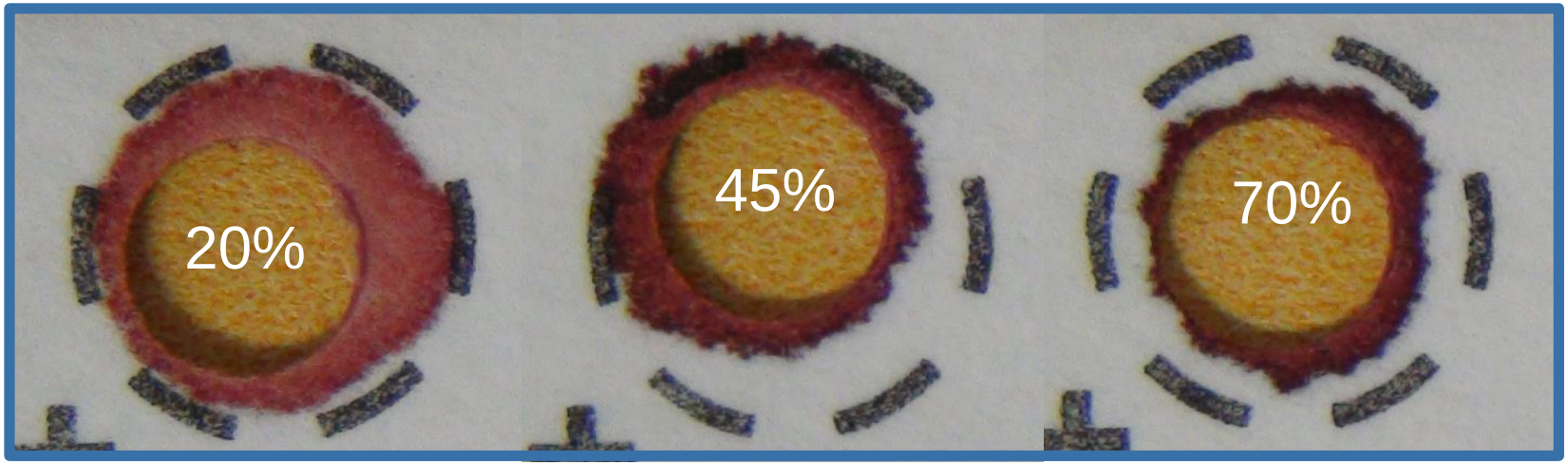
Problem!!!

Hematocrit

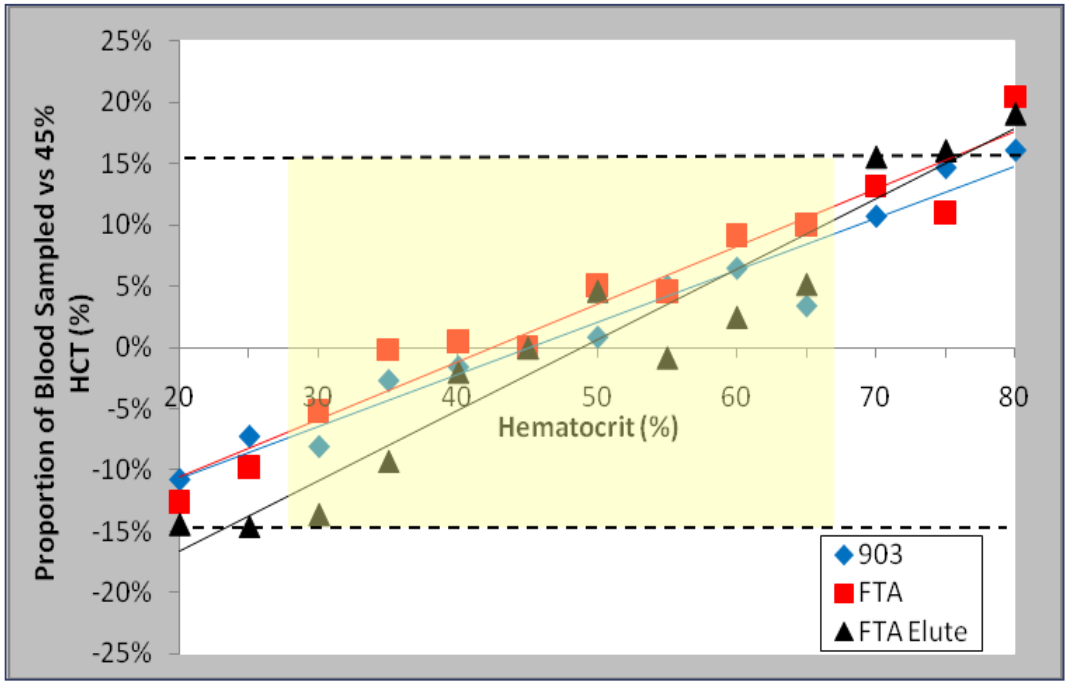


Woops!!!

Blood hematocrit affects the size of the derived blood spot



Effect of HCT on volume of blood sampled



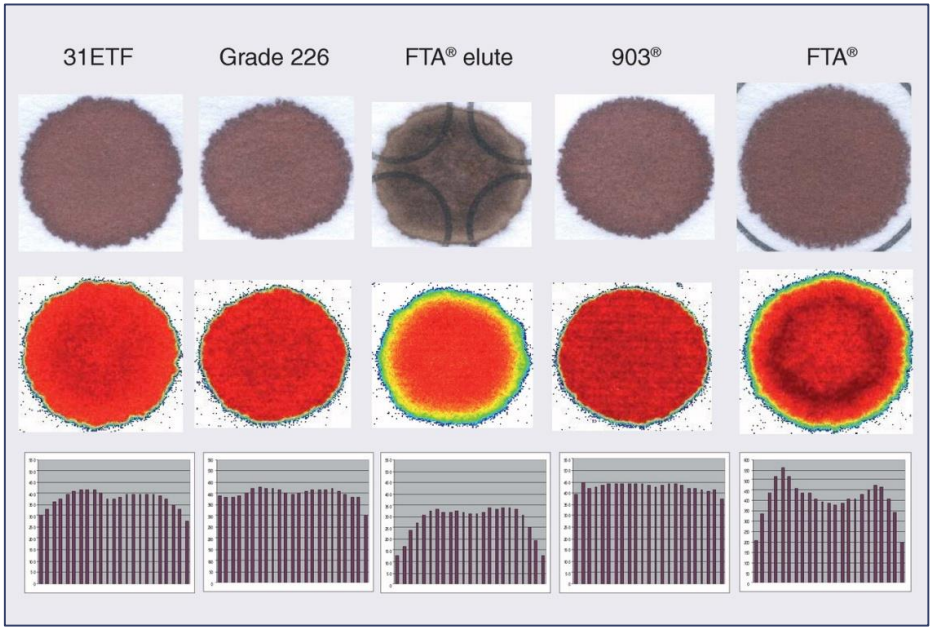
Fixed disc collected from spot with varying area

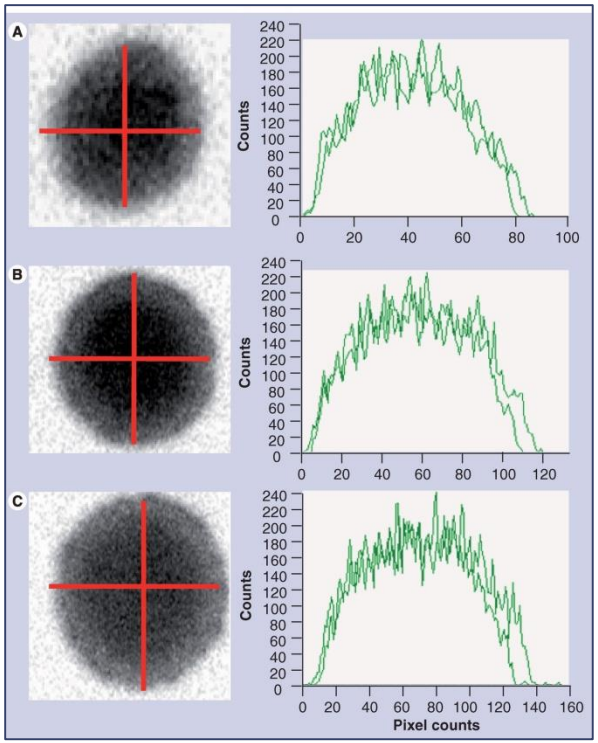
Denniff & Spooner (2010) *Bioanalysis* **2(8)** 1385-1395

Can be solved by spotting accurate volume and punching whole spot, or closely matching HCT of cal's & QC's to that of the samples

Wide range of hematocrits not often a major issue for tox studies

Spot homogeneity





Example radio histograms of the (A) 15-, (B) 30- and (C) 45-µl blood spots spiked with 14C radiolabeled UK-414495

Ren *et al,* (2010) *Bioanalysis* **2(8)** 1469-1475; Clark *et al* (2010*) Bioanalysis* **2(8)** 1477-1488

Resulting in……

Regulators (FDA & EMA) required collection & analysis of both wet and dry samples and demonstration of concordance in healthy volunteers and patient groups

Denniff & Spooner (2010) *Bioanalysis* **2(8)**, 1385-1395; O'Mara *et al* (2011) *Bioanalysis* **3(20)**, 2335-2347; de Vries *et al* (2013) *Bioanalysis* **5(17)**, 2147-2160; Cobb *et al* (2013) *Bioanalysis* **5(17)**, 2161-2169; Evans *et al* (2015) *AAPS J.* **17(2)**, 292-300; Kothare *et al* (2016) *AAPS J.* **18(2)** 519–527

Moving Beyond Conventional Dried Blood Spot Sampling

Overcoming the issues associated with

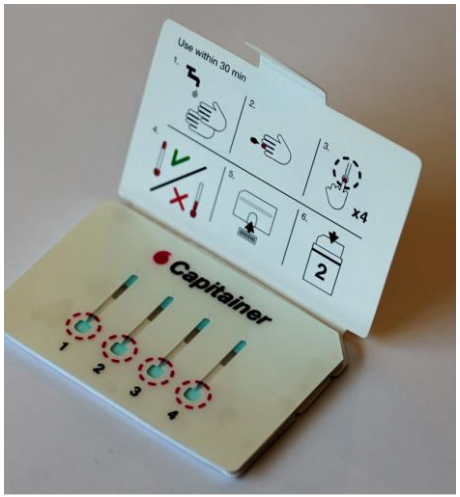
- Blood hematocrit
- Sample homogeneity

Whilst

- Delivering cost savings through home sampling and room temperature sample shipments
- Facilitating self sampling
- Integrating with systems for sample shipping / tracking and analysis

Patient Centric Technologies – Blood Collection*

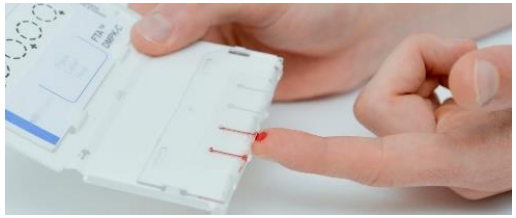
Capitainer
The Quantitative DBS System



https://capitainer.se/

neoteryx™
The promise of microsampling, delivered

https://www.neoteryx.com/



DBS System
HemaXis

http://hemaxis.com/

TRAJAN

https://www.trajanscimed.com/

*Other technologies are available

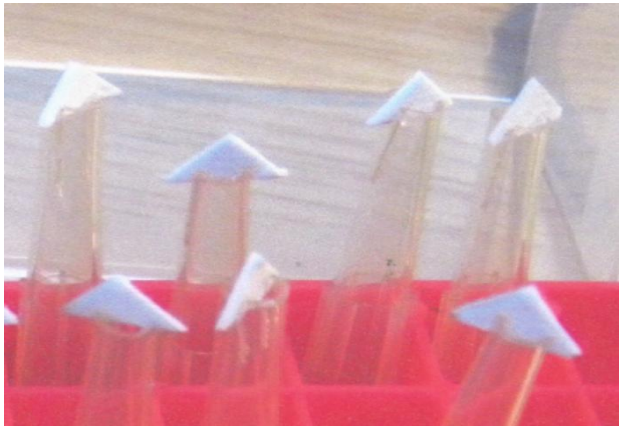
Volumetric Absorptive Microsampling - Mitra

neoteryx™
The promise of microsampling, delivered

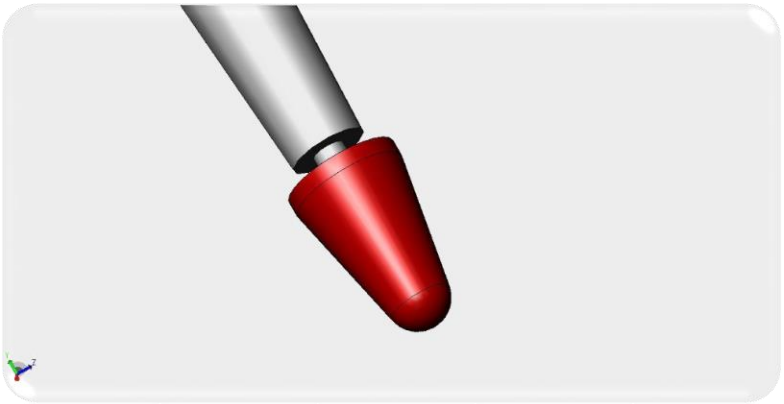
Hydrophilic porous material

Each Tip has a fixed, highly reproducible internal porous volume - 10 µL

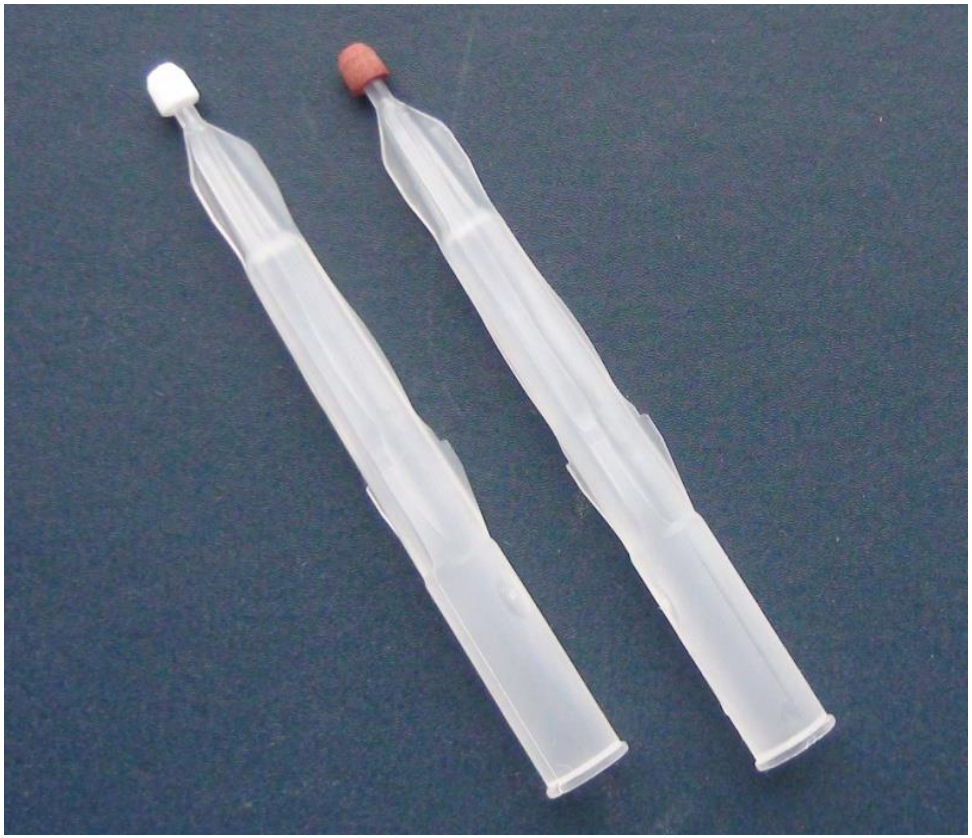
Rapid wicking
- Under 6 seconds



From humble beginnings....

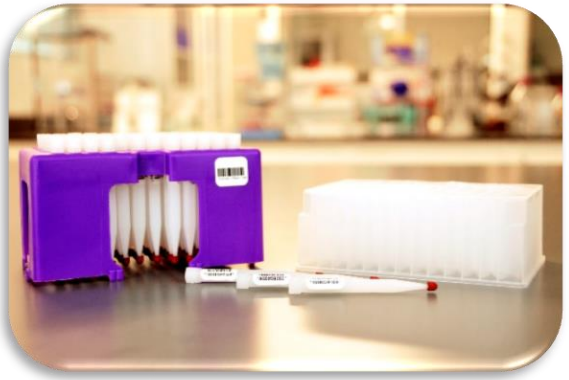


Sampler design



Mitra device formats available

clamshell device



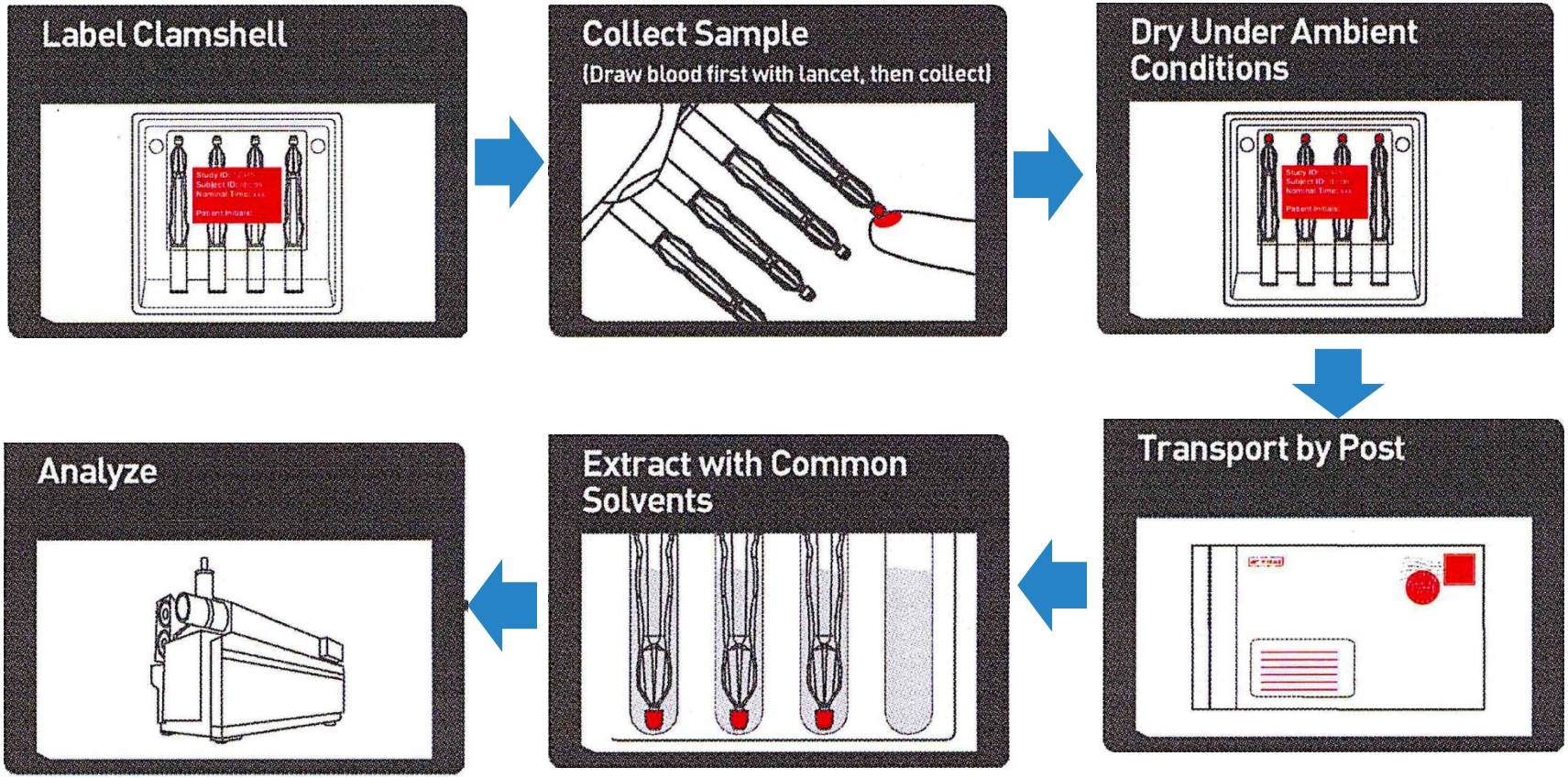
96-autorack device

cartridge device

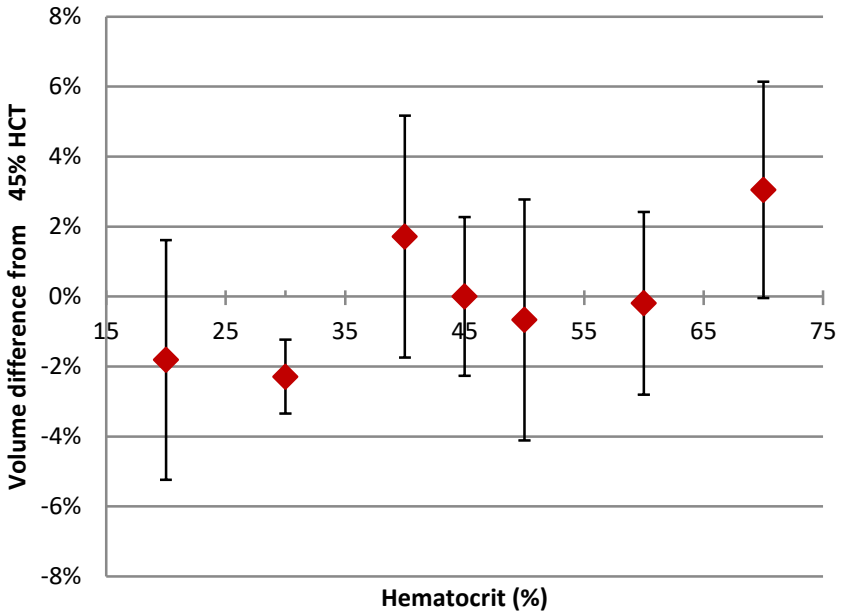
96-rack device

Simple to use

Simple workflow



Volumetric sampling performance

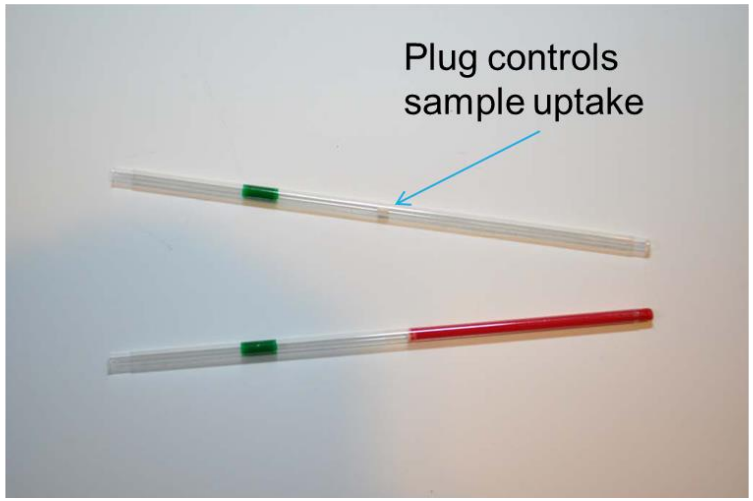


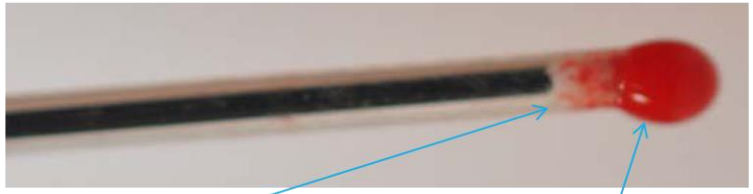
Human blood at different HCTs was spiked with ^{14}C caffeine
Tip oxidised to CO_2

Denniff & Spooner (2014) *Anal. Chem.* **86**, 8489-8495, Denniff *et al* (2015) *J. Pharm. Biomed. Anal.* **108**, 61-69, Spooner *et al* (2015) *Bioanalysis* **7(6)**, 653-659

What if you want wet blood?

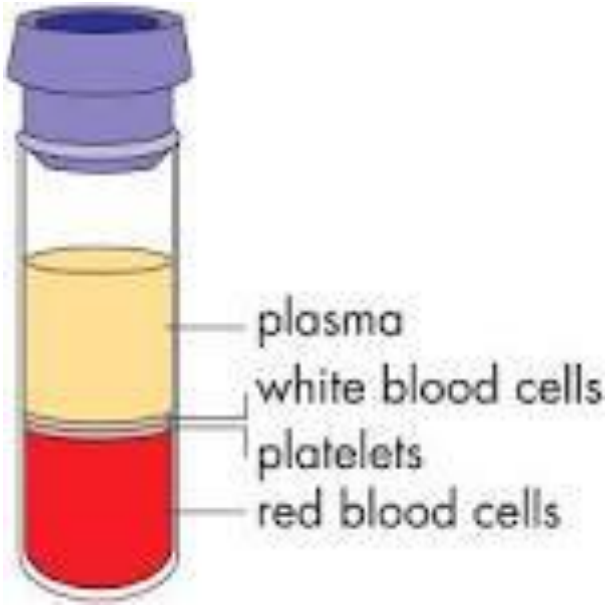
Blood / Water Microsample – Drummond Aquacap





Plunger advances plug which purges sample from walls of tube

Complete sample transfer



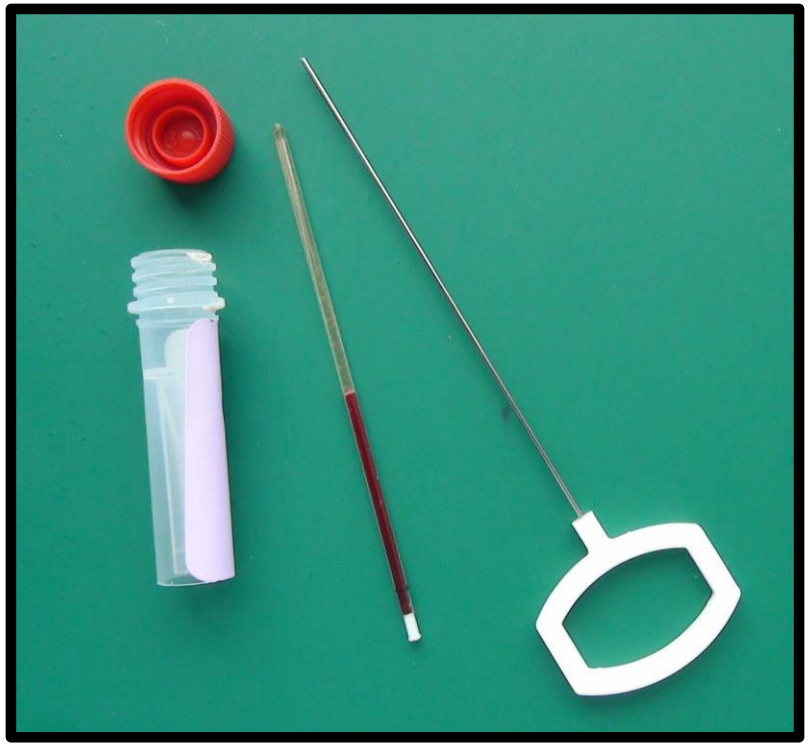
But what if you want plasma rather than whole blood??!!

Emmons & Rowland (2010) *Bioanalysis* **2(11)** 1791-1796

Drummond Plasma Gel Separator Microsampling Capillary

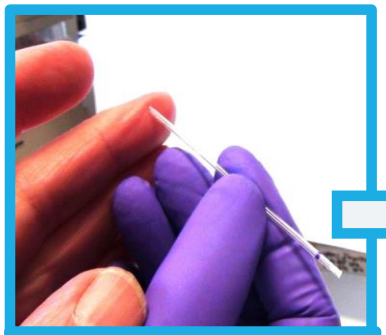
Capillary

- Glass capillary
- Mylar film coat (strength & safety)
- Internal EDTA coating
- Porous plug
- Thixotropic gel



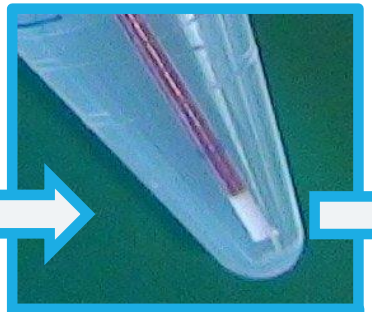
Bowen *et al* (2013) *Bioanalysis* **5(9)**, 1131-1135

Overview – Drummond Sample Collection & Processing



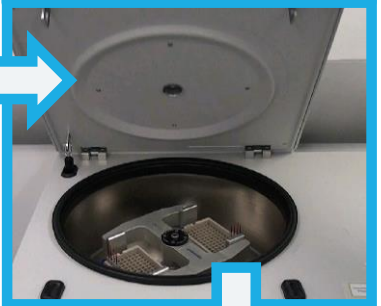
Collect 70 µL blood sample into capillary

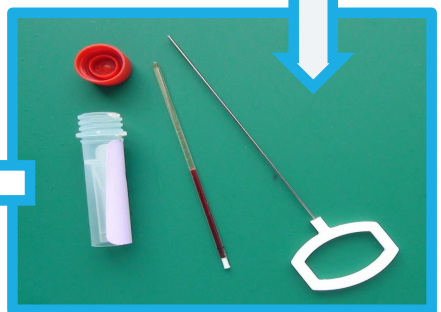
Protect filled capillary in labelled Falcon tube



Porous plug swells & seals capillary on contact with blood

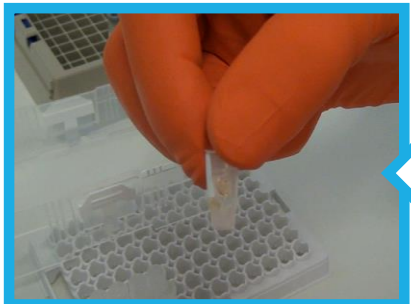
Centrifuge samples at ≥1500 rfc (g) for 10 mins at ambient temp





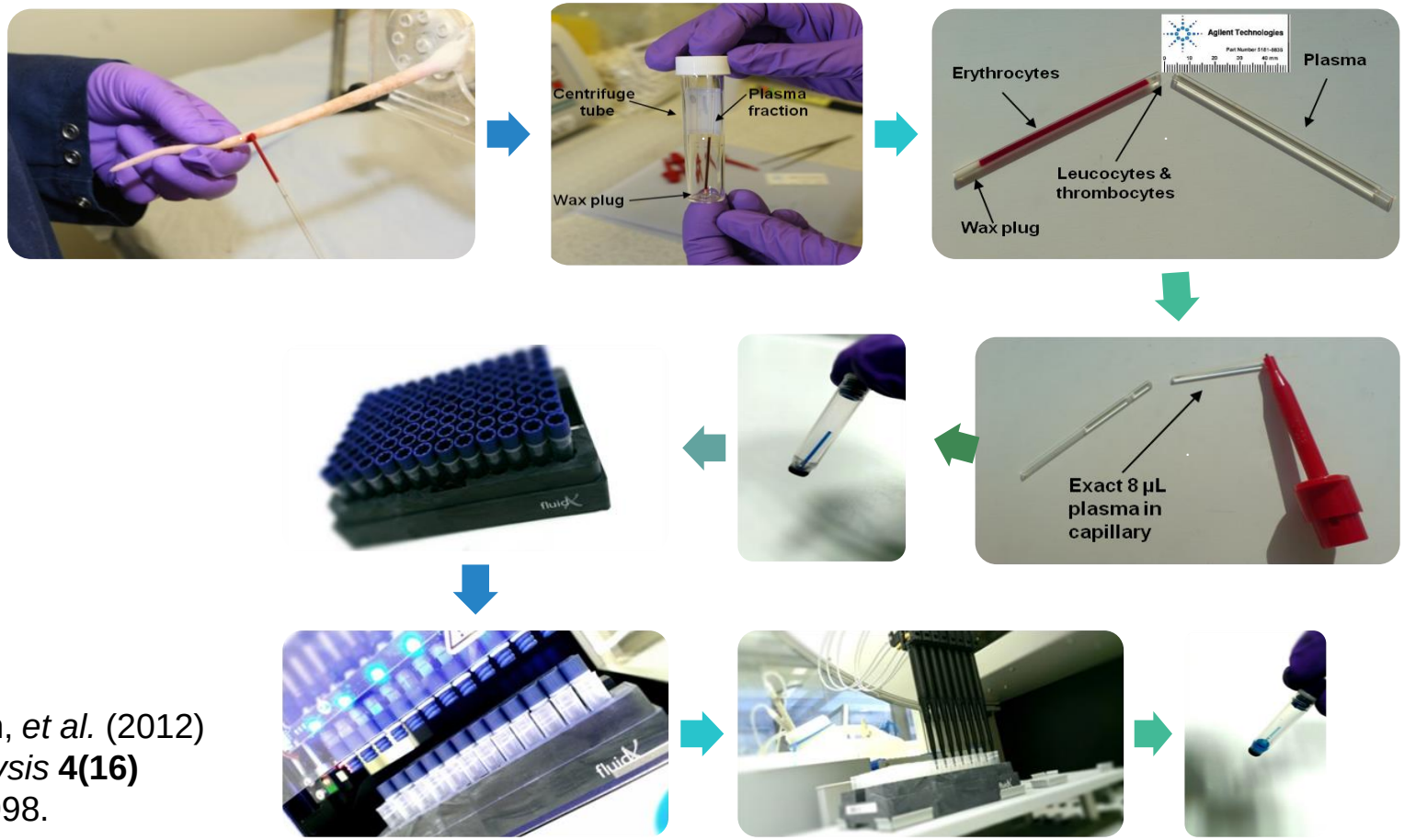
Plasma & blood separated in capillary. Pushing from plug end expels plasma

Use Wiretrol to expel 25-30 µL plasma into a labelled tube & freeze



Defrost & analyse 7 µL aliquot

Sample collection & processing



Jonsson, *et al.* (2012) *Bioanalysis* **4(16)** 1989-1998.

Regulatory Landscape

Pre-Clinical

- ICH Q&A on Microsampling as part of ICH S3A Guideline (Nov 2017)
- Also See
  - Beharry (2010) *Bioanalysis* **2(8)**, 1363–1364
  - Viswanathan (2012) *Bioanalysis* **4(12)**, 1417–1419

Clinical

- FDA guidance provided in latest BMV document (May 2018)
  - *"This validation should address, at a minimum, the effects of the following issues: storage and handling temperatures, homogeneity of sample spotting, hematocrit, stability, carryover, and reproducibility, including ISR"*
  - *"Correlative studies with traditional sampling should be conducted during drug development"*
  - *"Sponsors are encouraged to seek feedback from the appropriate FDA review division early in drug development"*
- Also see
  - Evans, *et al* (2014) *The AAPS Journal* **17(2)**, 292-300
  - Kothare, *et al* (2016) *The AAPS Journal* **18(2)**, 519–527

Summary

Numerous approaches to microsampling

- Select the one that fits best with your organisation, experimental, quality and logistic requirements
- Will require a lot of change control and training

The field and technology is developing quickly

You are not alone……

Consider carefully the journey of the sample and the fate of the analyte(s) when validating / qualifying methods

Practical Considerations for the Implementation of Microsampling

Melanie Anderson (Merck)

What is the need? What question are we answering? Can micro sampling meet this need?

- Program/Institutional Needs
  - Animal Studies – 3Rs, subject number reduction, reduced variability
  - Matrix requirements
  - At home sampling benefits
  - Specific indications – pediatrics, migraine, cancer, therapeutic drug monitoring

The technology is disruptive to existing workflows across the organization – the need must be great

Micro sampling Feasibility

Scientific Feasibility

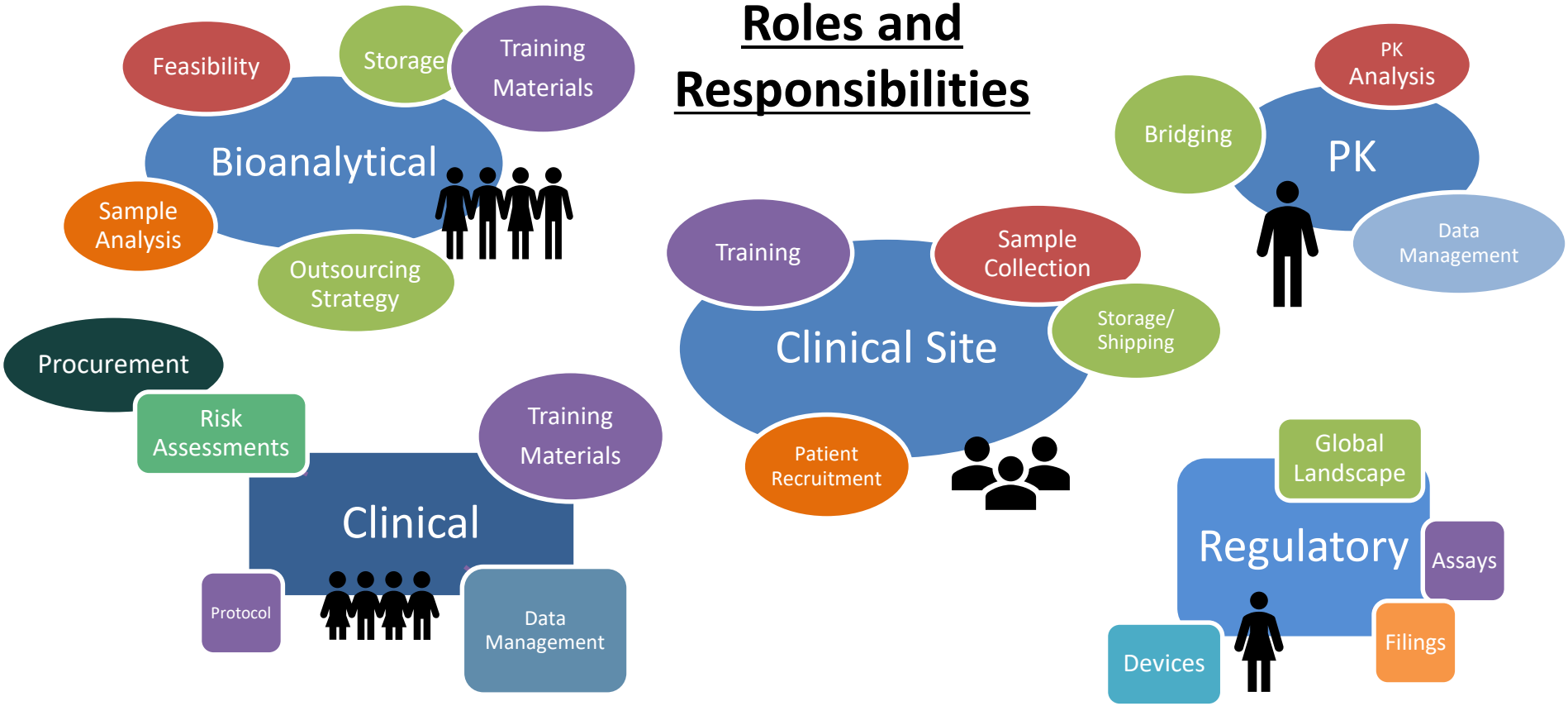
- Metabolites
- Blood to Plasma Ratio
- Stability
- Extractability
- Assay sensitivity

Logistical Feasibility

need strategic involvement across the organization

- Protocol Authoring
- Sample Collection Training
- Sample Quality
- Sample Management
- Sample Analysis
- Automation
- Regulatory

Roles and Responsibilities



Clinical & Pharmaceutical Solutions through Analysis
October 15-18, 2018
Langhorne, PA

Practical Considerations for Development & Qualification / Validation of Bioanalytical Methods for Studies Where Microsampling is Used

Tim Olah (Bristol-Myers Squibb) & Enaksha Wickremsinhe (Eli Lilly & Co)

Practical considerations for development and qualification / validation of bioanalytical methods for studies where microsampling is used

- Delegates and instructors will discuss what experiments are required to ensure that quantitative data of the appropriate quality is generated when using a variety of microsampling approaches
- Discussion will revolve around the specifics of the experiments that are different to those performed for routine bioanalytical method development, qualification and validation

Bioanalytical challenges (EW) (microsampling/dried matrices/home sampling)

- **Preparation of Standard Curves and QCs**
- **Assay sensitivity** – can you get the needed LLOQ?
- **Additional validation experiments –** depending on technique
- **Account for stability during collection/storage/transit**
  - temperature, humidity, drying time, shipping conditions.
- **Addition of Internal Standard** – in extraction solvent?
- **More time and effort needed in BioAnalytical lab**
  - not in 96-well format, AUTOMATION
- **Overall BioAnalytical cost higher?**

Bioanalytical challenges (TO)
Conduct unique experiments beyond routine

- **Bridging studies with current collection practices?**
  - Compare DBS with blood lysate and/or wet or dry plasma?
    - Conduct on incurred samples (n ≥ 20)?
    - Cost to perform and impact of mismatched data sets?
    - Identify the deficiency of the assay or operational error?
  - Evaluate effect of shipping, storage, and handling temperatures
  - Assess homogeneity of DBS sample spotting
  - Study impact of hematocrit within reasonable levels?
  - Carryover from puncher?

Practical Considerations for the Use of Microsampling in Clinical Studies

Kevin Bateman (Merck), Tim Olah (Bristol Myers Squibb), Enaksha Wickremsinhe (Eli Lilly & Co) & Neil Spooner (Spooner Bioanalytical Solutions)

Regulatory

FDA guidance on Dried Blood Spot approaches provided in latest BMV document (May 2018)

- *"Correlative studies with traditional sampling should be conducted during drug development"*
- *"Sponsors are encouraged to seek feedback from the appropriate FDA review division early in drug development"*

Also see

- Evans, *et al* (2014) *The AAPS Journal* **17(2)**, 292-300
- Kothare, *et al* (2016) *The AAPS Journal* **18(2)**, 519–527

Bridging (Correlative) Studies

- What?
  - Wet vs dry
  - Blood vs plasma
  - Capillary vs venous
  - Patients vs healthy volunteers
- How to show concordance?

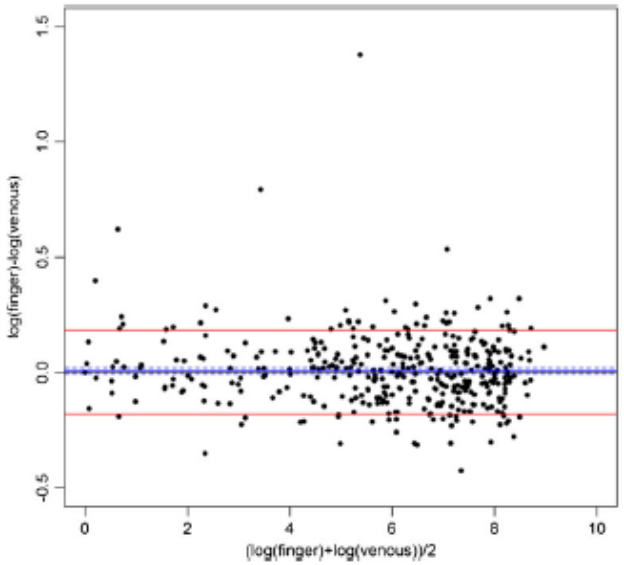


Fig. 6. Bland–Altman plot comparing results obtained from fingertip and venous sampling

Approach for Obtaining Quality Blood Samples

- What patients?
  - Pediatric
  - Critically ill
  - Other
- Technology for obtaining blood
  - Finger / heel prick
  - Venous
  - Scavenged
  - Other
- Blood sampling technology
  - DBS
  - Other

Training

- Who?
  - Patients & carers
  - Clinical practitioners
- Where?
  - Home
  - Clinic
- How?
  - Videos
  - Guides
  - Qualification
  - Ongoing training / support

Emerging Microsampling Technologies

Kevin Bateman (Merck)

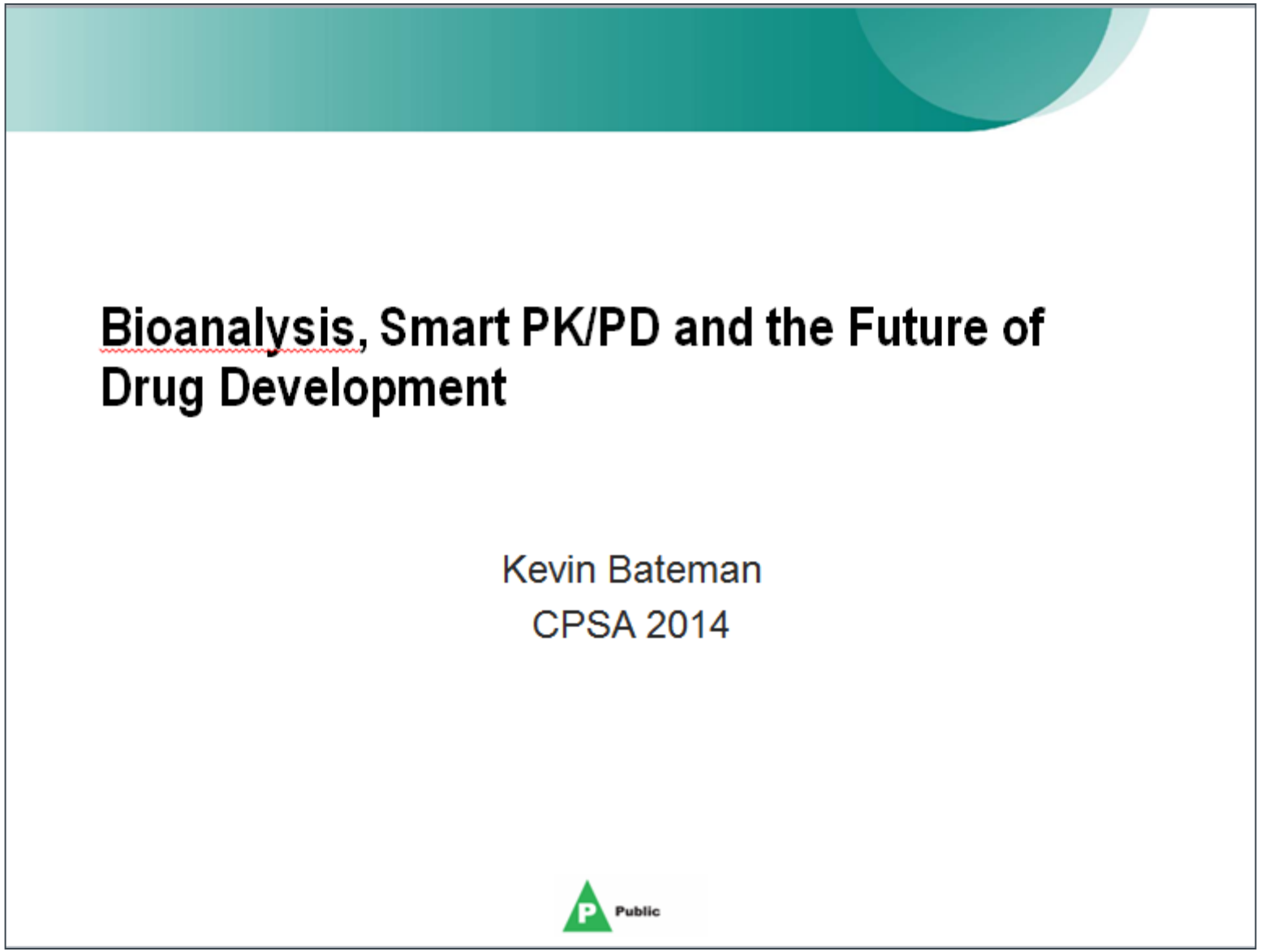
SMART TRIALS: MOVING FROM SITE-CENTRIC TO PATIENT-CENTRIC CLINICAL TRIALS

Kevin Bateman

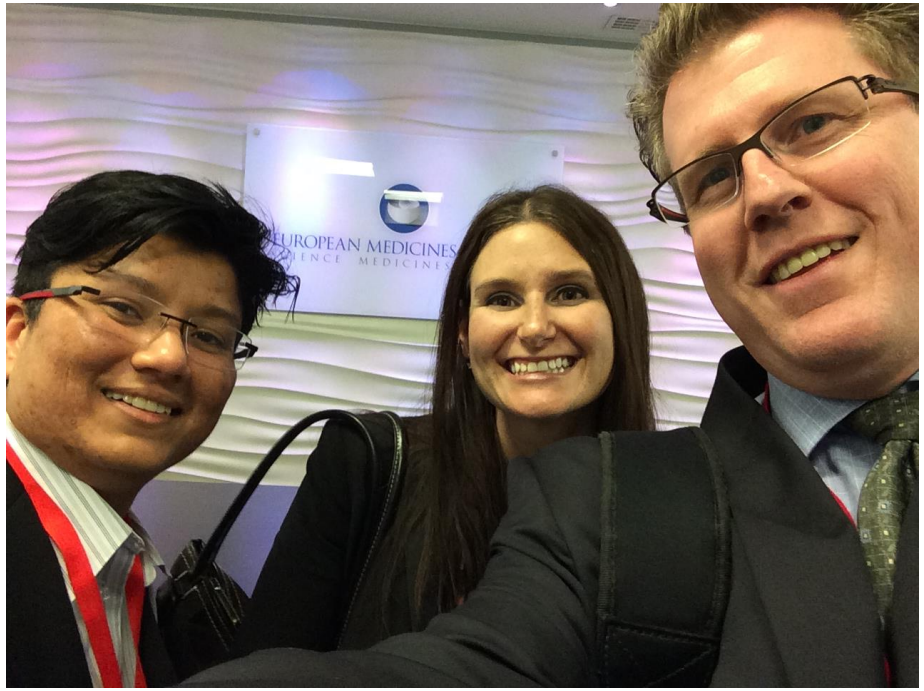
CPSA USA

October 17th, 2018

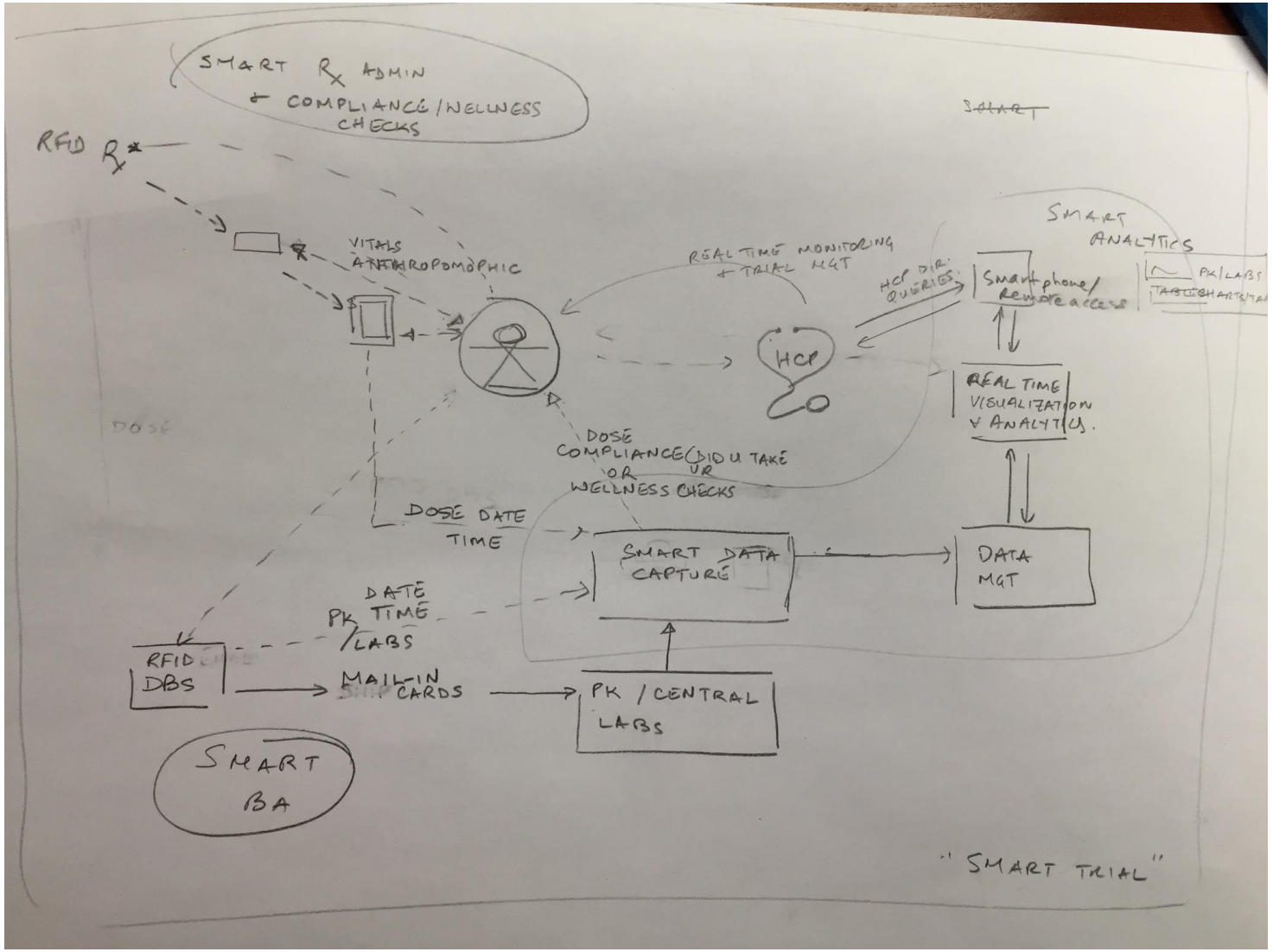
Not so long ago…in 2014



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

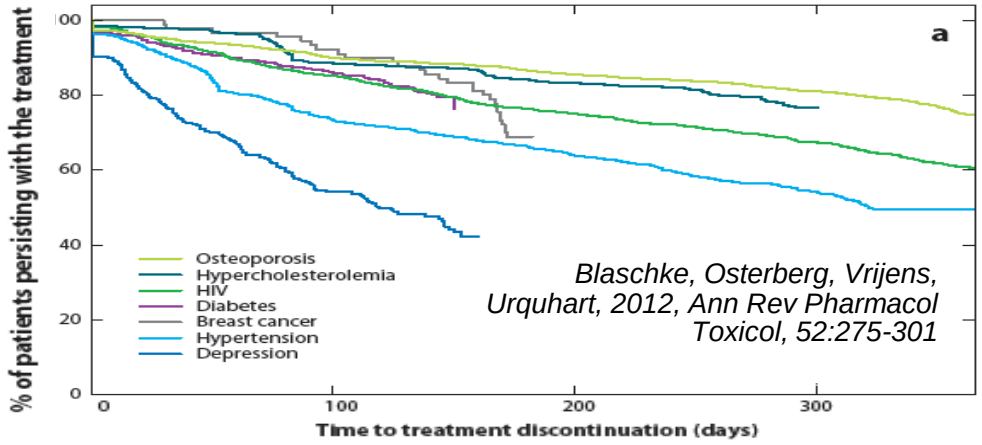
- Patient recruitment often limited to those that live near clinical site
- Patient and family burden
- Static “snapshots” of data
- High cost for each visit
- Limited feedback of data during the study

Operational Inefficiencies

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

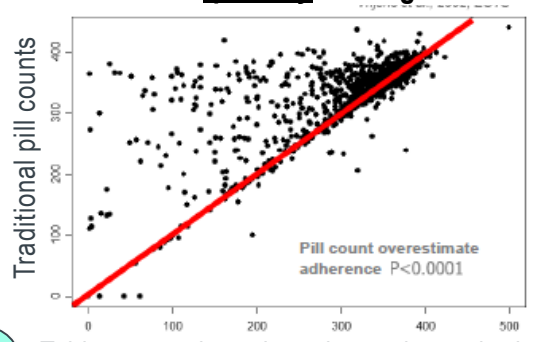
Current paradigm does not take advantage of emerging trends in digital health technologies that can drive a more patient-centric approach

Adherence & Data Inaccuracies



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

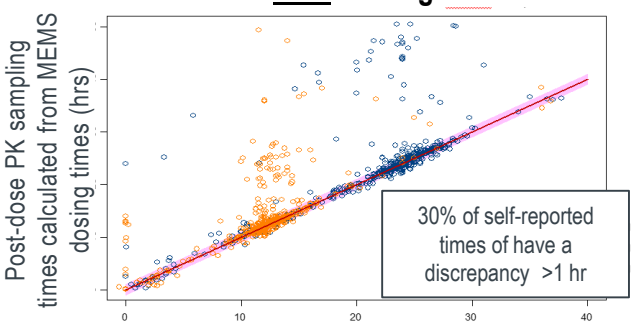
Bias in quantity of drug taken



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)

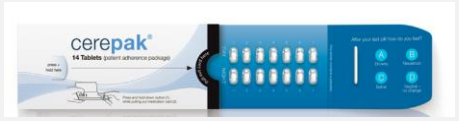
Tousset. et. al. 2005, PAGE

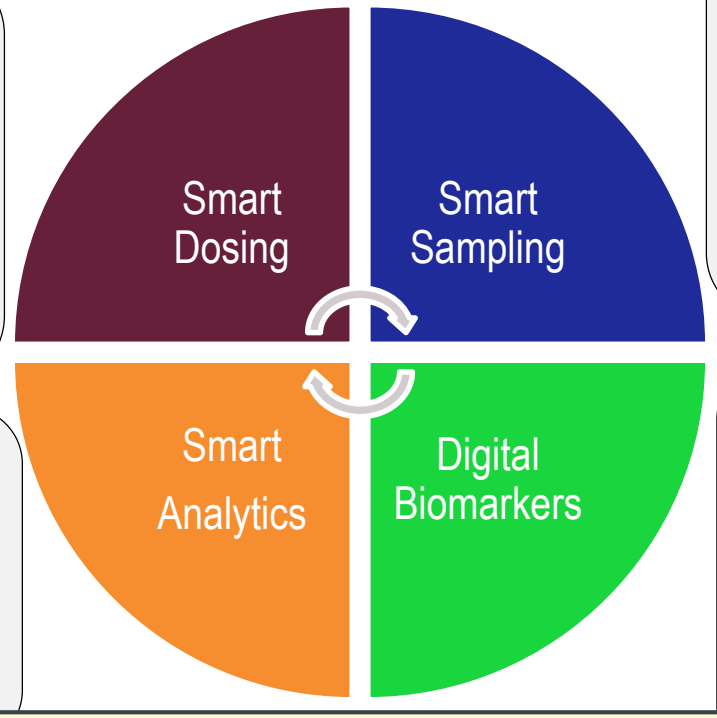
MERCK INVENTING FOR LIFE

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

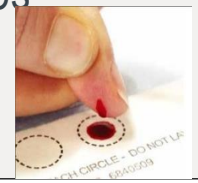
Smart Trials is a cross-functional, multi-year innovation project at Merck & Co., Inc. aimed at **enriching clinical trial datasets** and enabling more **rapid and informed clinical decisions** through a **patient-centric approach**

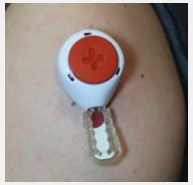
Smart Dosing: technologies to record and transmit dosing information (i.e. if and when the patient took the drug)



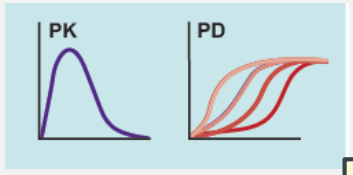


Smart Sampling: technologies for use in the outpatient setting to collect PK, PD, or biomarker samples coupled with date/time stamps





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.

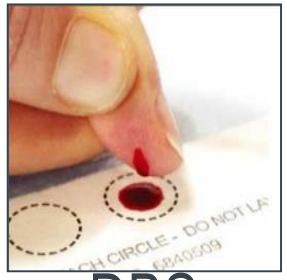
MERCK INVENTING FOR LIFE

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™

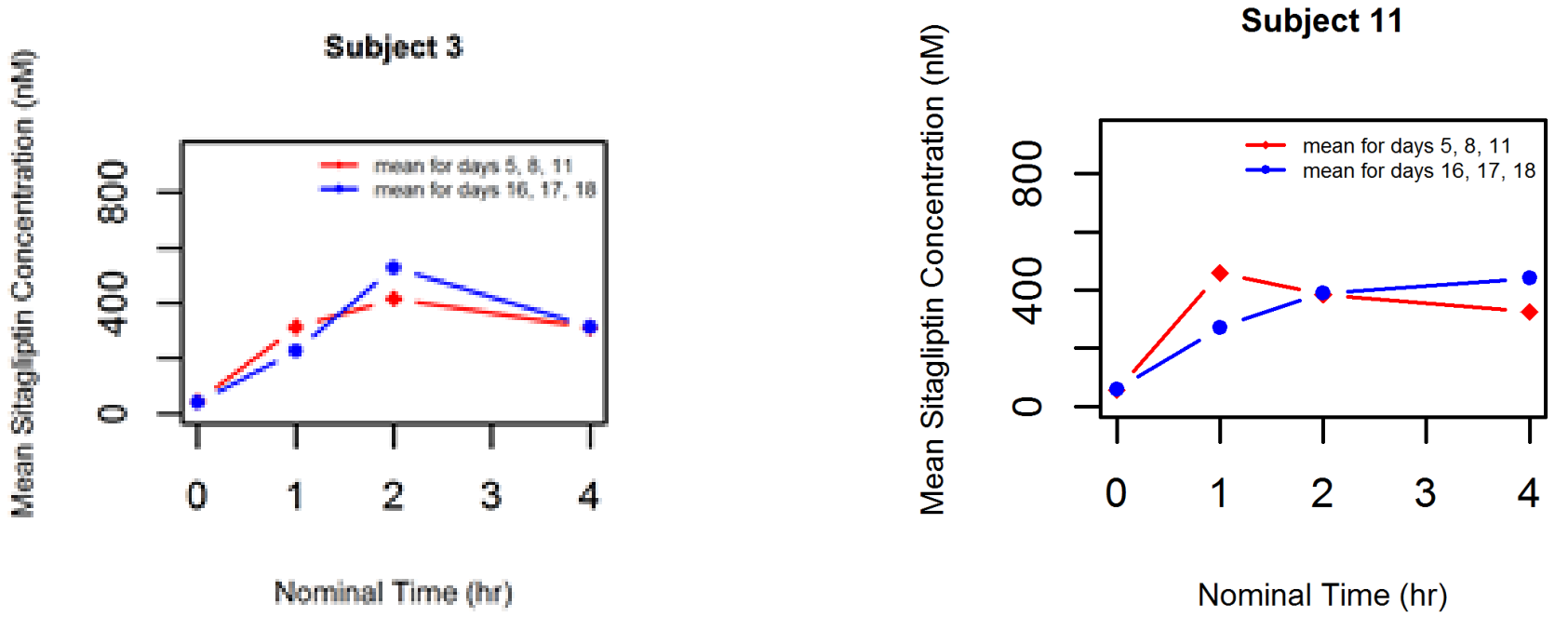
HemoLink

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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0014	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
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	09-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	10-OCT-2016	11-OCT-2016	12-OCT-2016	12-OCT-2016	12-OCT-2016	13-OCT-	14-OCT-2016	14-OCT-2016	0

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**

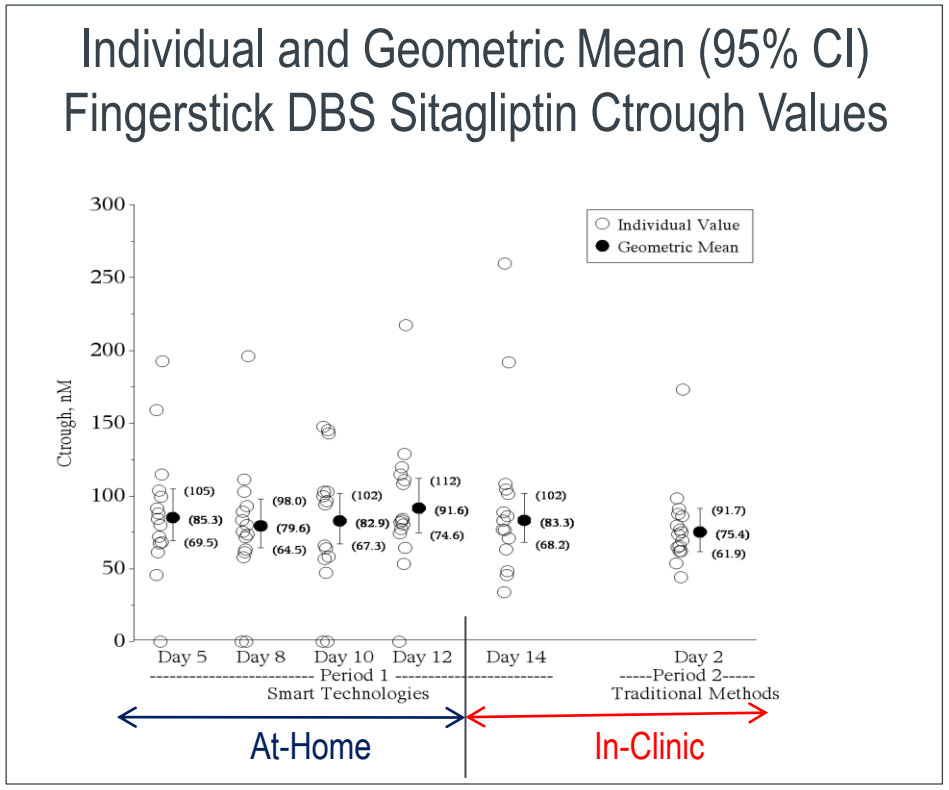
	Sitagliptin Concentration (ng/mL)												
			Ctrough	C8hr	Ctrough	C8hr	Ctrough	C4hr	Ctrough	C1hr	C8hr	Ctrough	C8hr
AN	Day 1, 0hr	Day 1, 1hr	Day 5, 0hr	Day 5, 8hr	Day 8, 0hr	Day 8, 8hr	Day 10, 0hr	Day 10, 4hr	Day 12, 0hr	Day 12, 1hr	Day 12, 8hr	Day 14, 0hr	Day 14, 8hr
1	BLQ	335	19	BLQ	BLQ	BLQ	BLQ	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

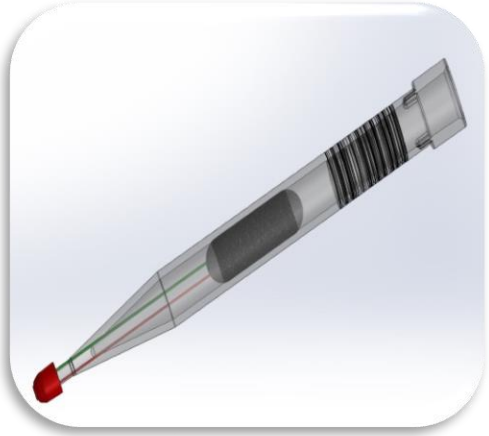


- **eDiary data:** Two subjects had missing eDiary entries for collected PK samples
- **Comparison of PK & Dosing Data:** Undetectable sitagliptin concentrations for at-home samples collected from 2 subjects, despite reported dosing via Smart Packaging & eDiary
  - In one case, DNA profiling confirmed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

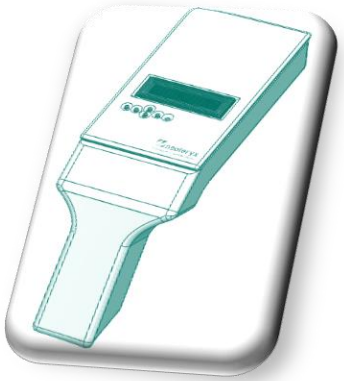
- Sitagliptin concentrations from samples collected at-home were generally similar to those collected in-clinic
- Missing eDiary data highlight importance of adding automated date/time stamps
- Smart Packaging is an improved yet imperfect indicator of adherence
- DNA profiling can be a useful tool as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

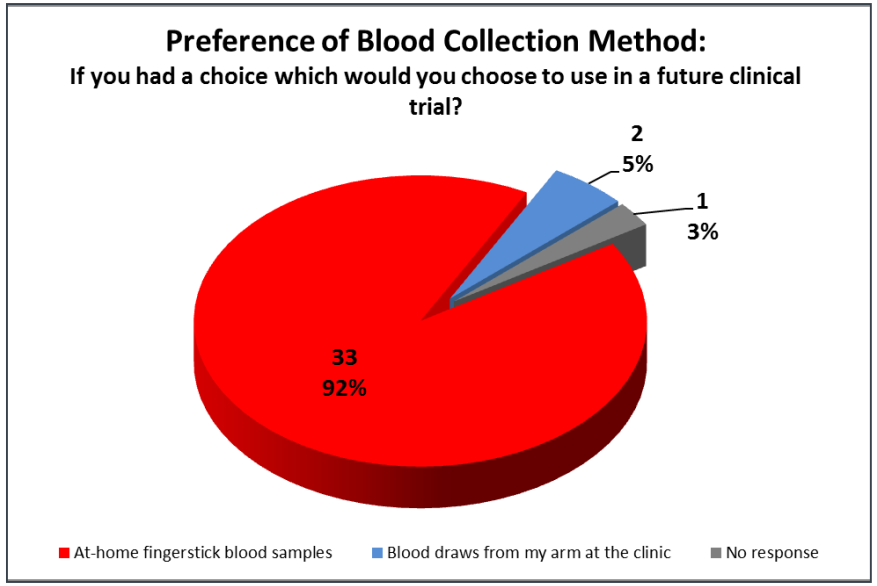


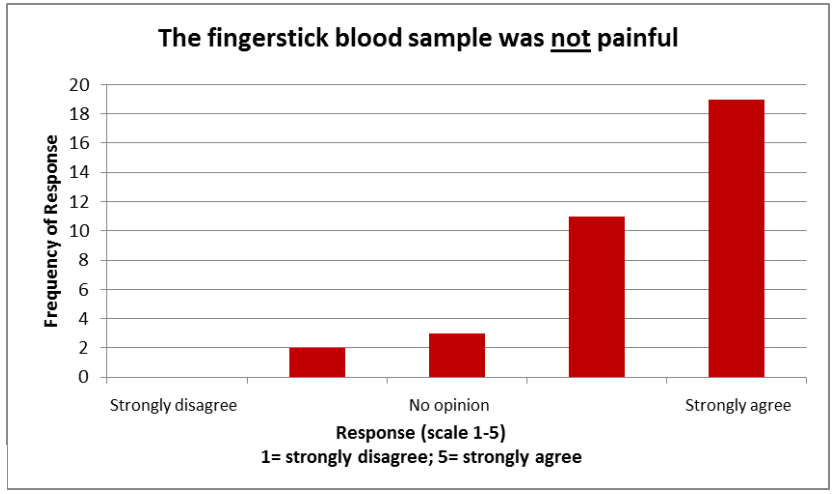
Rendering of Potential Commercial Product

13

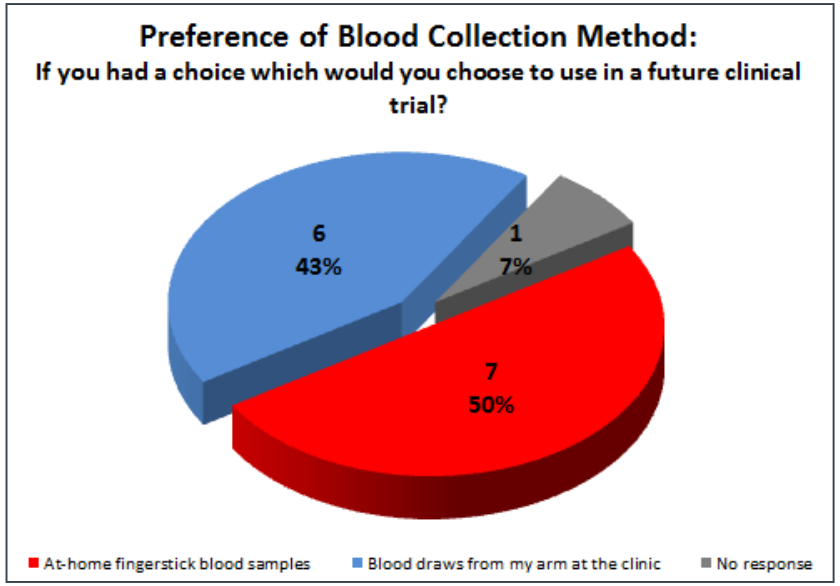
Smart Sampling: Questionnaire Results

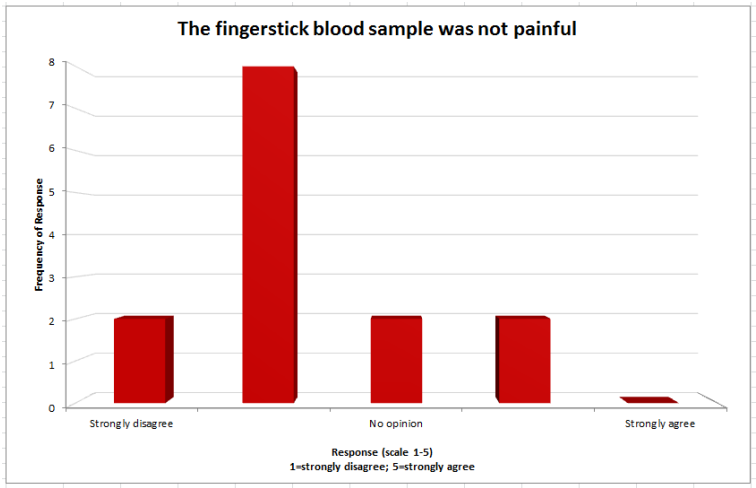
MK-X Study (1 sample/day, n=36)





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





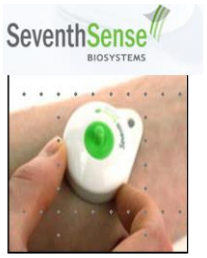
Reduced frequency of fingerstick sampling may result in less pain and help drive subject preference toward at home fingerstick sampling

Smart Sampling: Questionnaire Results

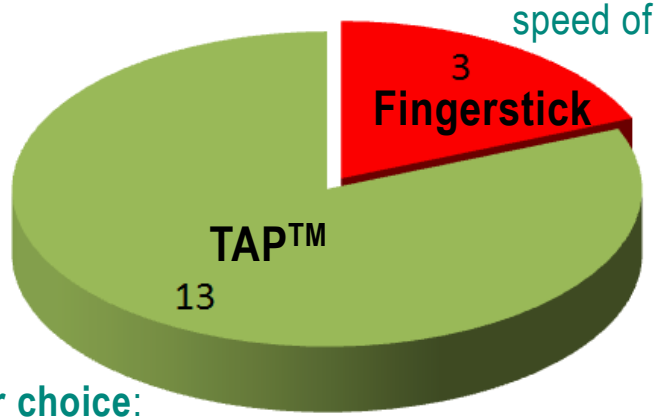
TAP™ device

- 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

If you had a choice, which would you choose to use in a future clinical trial?



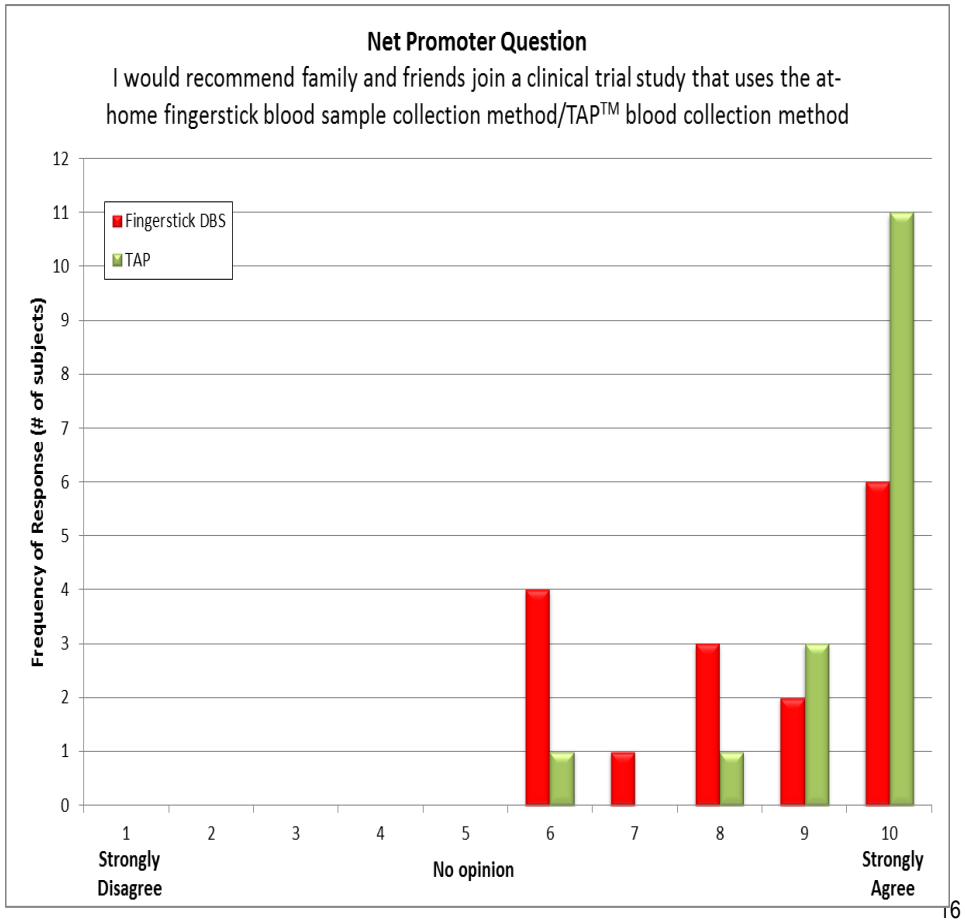
Microneedle-based TAP™ device



Rationale for choice: speed of collection

Fingerstick via lancet

Rationale for choice: less painful

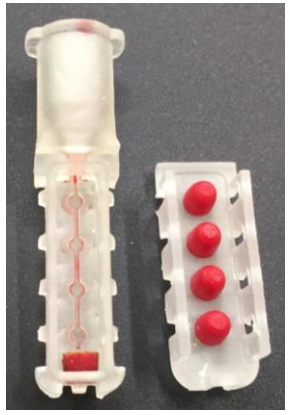


Less painful methods of sampling may be beneficial in driving subject preference for at-home sampling

Smart Sampling Pilot #3: Fingerstick, Venous, Hemolink

Fingerstick via lancet

Venous



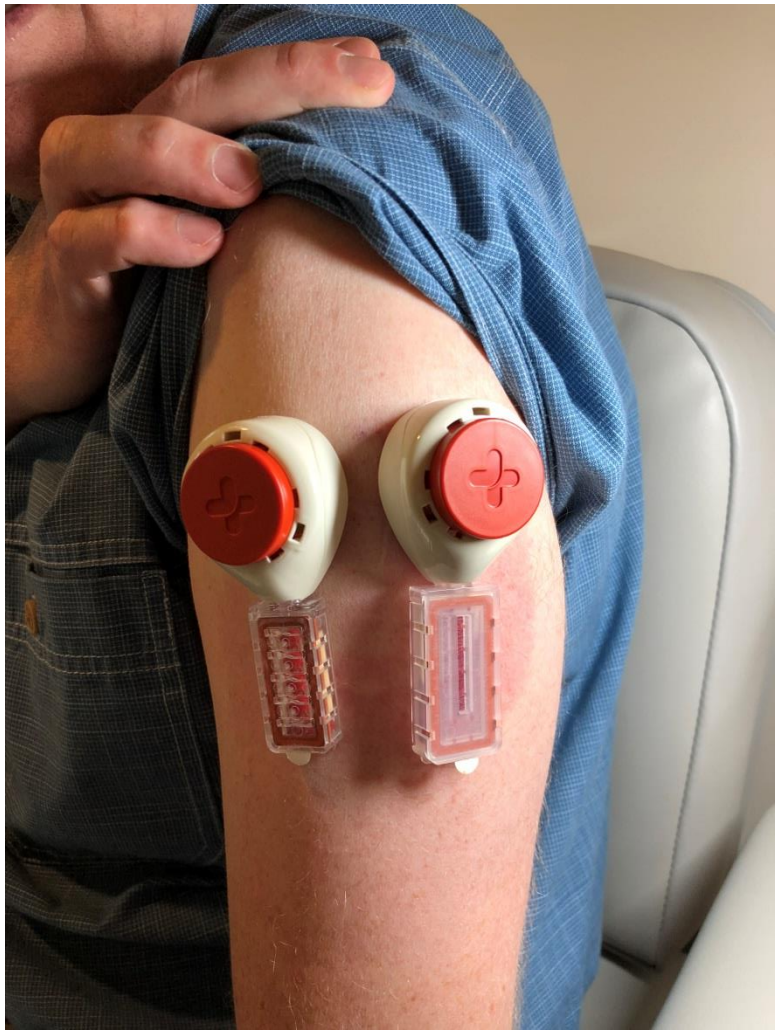
Tasso Hemolink with Mitra

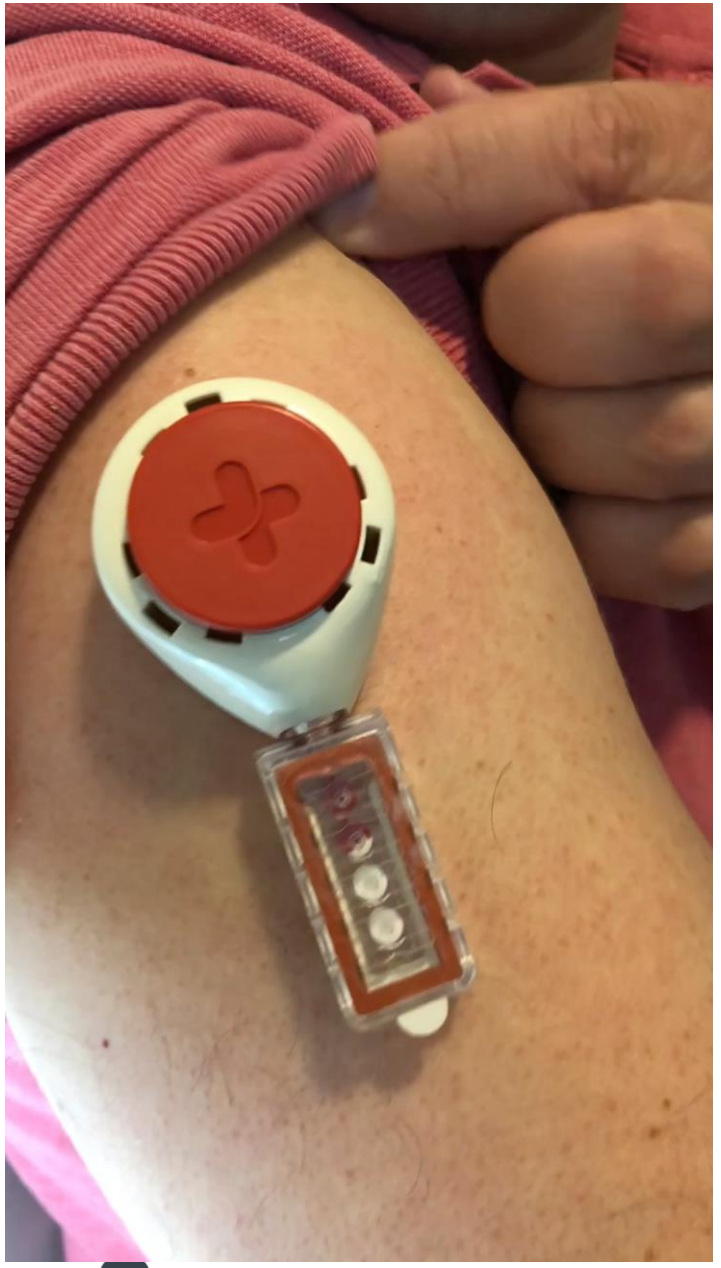
Part 1

- 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





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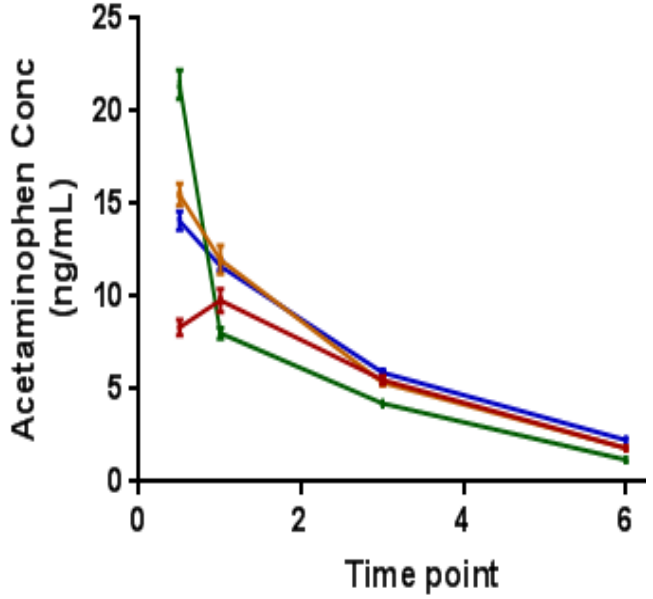
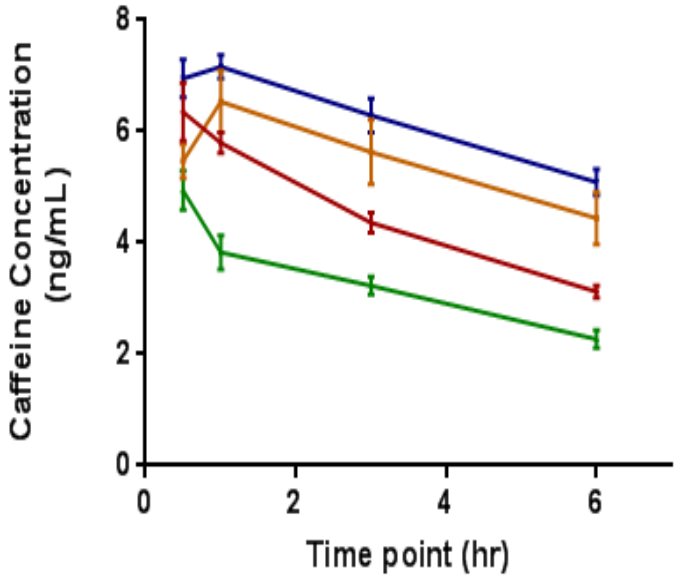
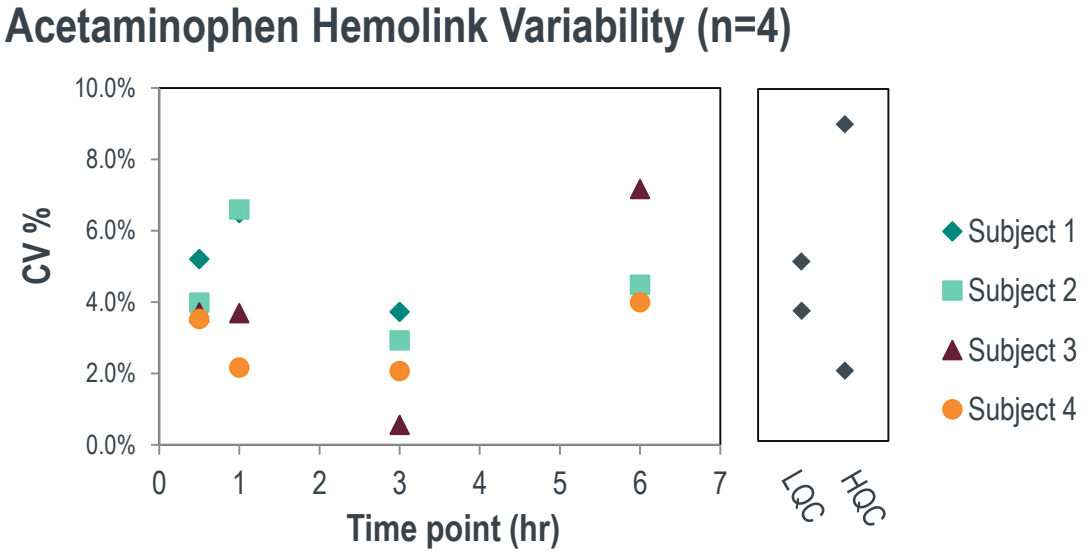
Smart Sampling Pilot #3: Hemolink

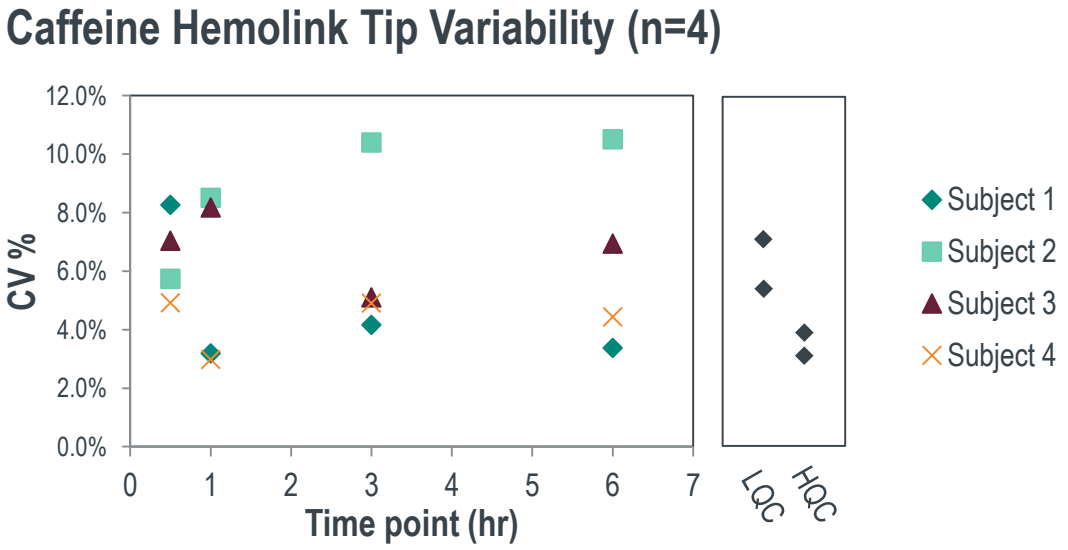
Part 1

- 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









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Smart Sampling Pilot #3: Hemolink

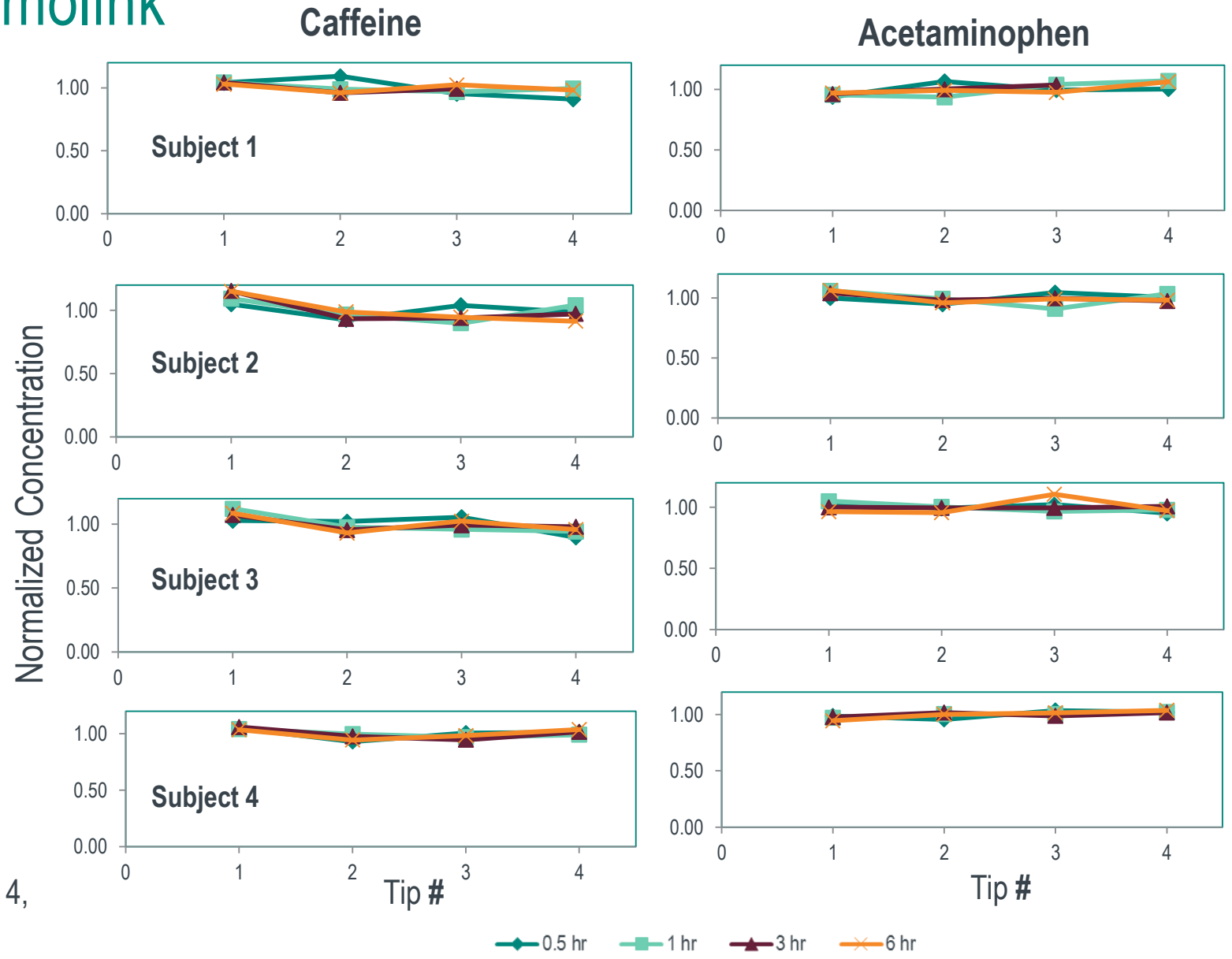
Part 1

- 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

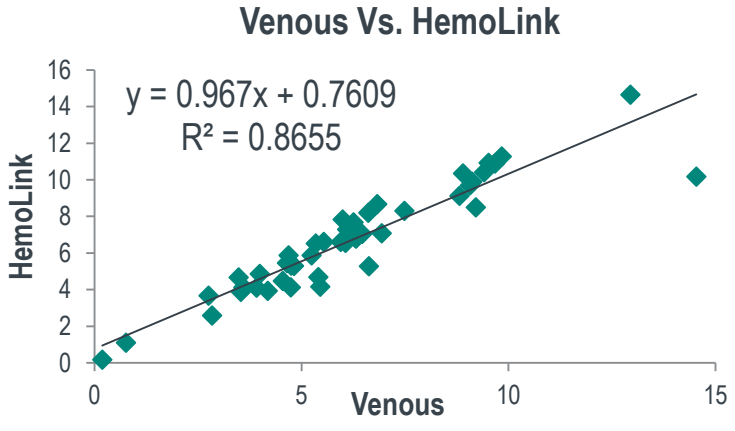


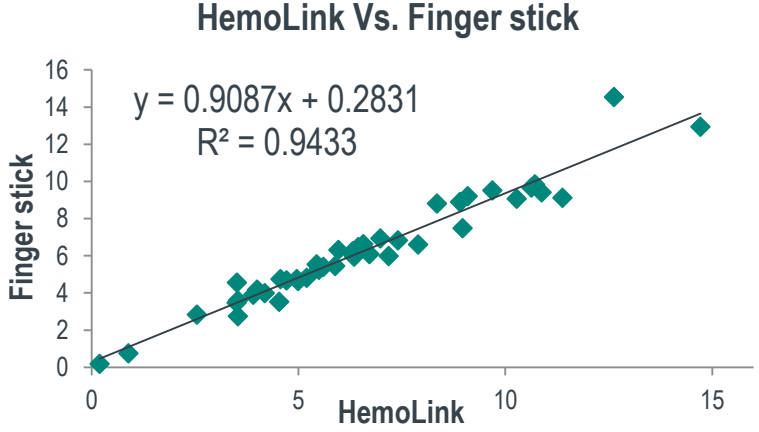
Smart Sampling Pilot #3: Fingerstick, Venous, Hemolink

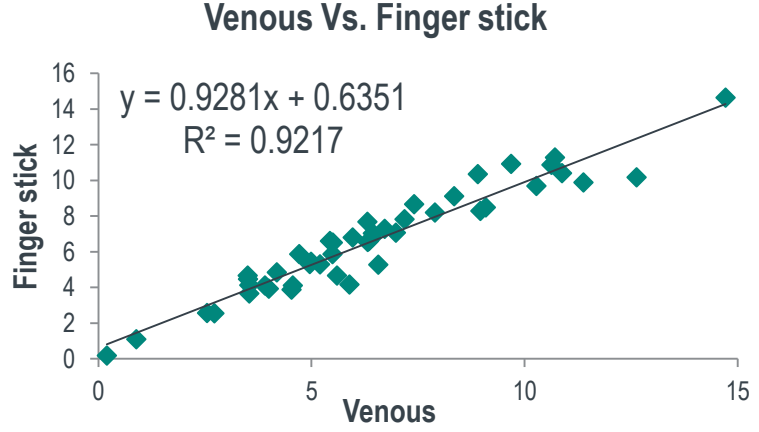
Part 2

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

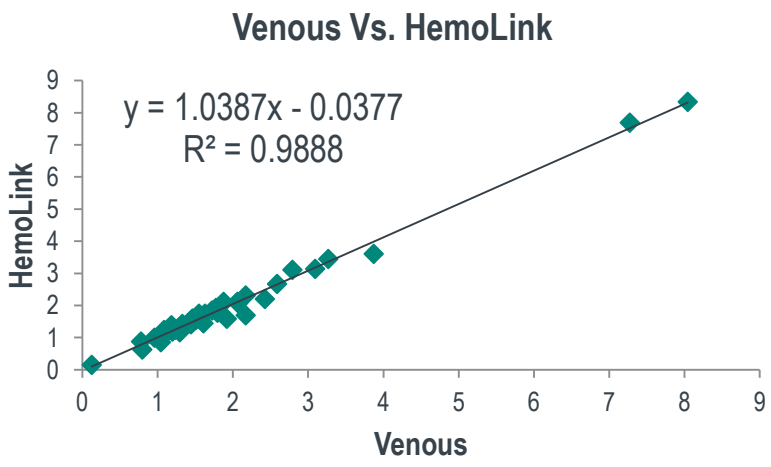
Acetominophen

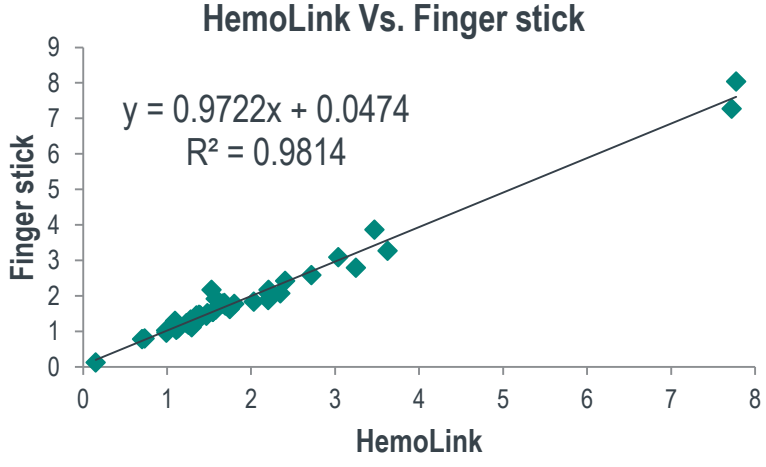


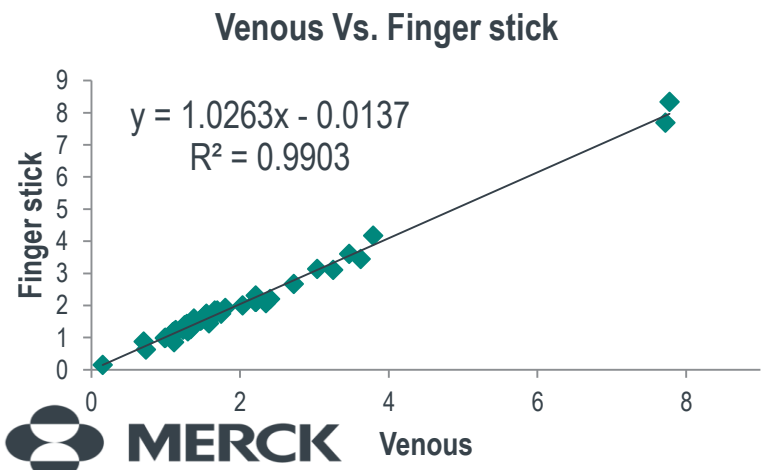




Caffeine







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Smart Sampling Pilot #3: Fingerstick, Venous, Hemolink

Part 2

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

Acetaminophen n=23	1 hour			2 hour		
	Fingerstick	Hemolink	Venous	Fingerstick	Hemolink	Venous
Total Mean	6.70	6.52	6.65	6.18	5.91	6.57
Total Std Dev	3.26	3.18	3.25	2.76	2.37	2.56

% Difference – 1hr	
Fingerstick/Hemolink	2.7%
Hemolink/Venous	-2.0%
Fingerstick/Venous	0.7%

% Difference – 2 hr	
Fingerstick/Hemolink	4.4%
Hemolink/Venous	-10.6%
Fingerstick/Venous	-6.2%

Caffeine n=23	1 hour			2 hour		
	Fingerstick	Hemolink	Venous	Fingerstick	Hemolink	Venous
Total Mean	1.93	1.83	1.97	2.00	2.01	2.04
Total Std Dev	1.50	1.50	1.61	1.42	1.34	1.40

% Difference – 1hr	
Fingerstick/Hemolink	5.3%
Hemolink/Venous	-7.1%
Fingerstick/Venous	-1.8%

% Difference – 2 hr	
Fingerstick/Hemolink	-0.1%
Hemolink/Venous	-1.9%
Fingerstick/Venous	-2.0%

Key Take-Aways

There are no significant quantitation difference for acetaminophen and caffeine for VAMS samples when using venous, finger stick, or Tasso HemoLink collection. Variability is similar between all sampling techniques.

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

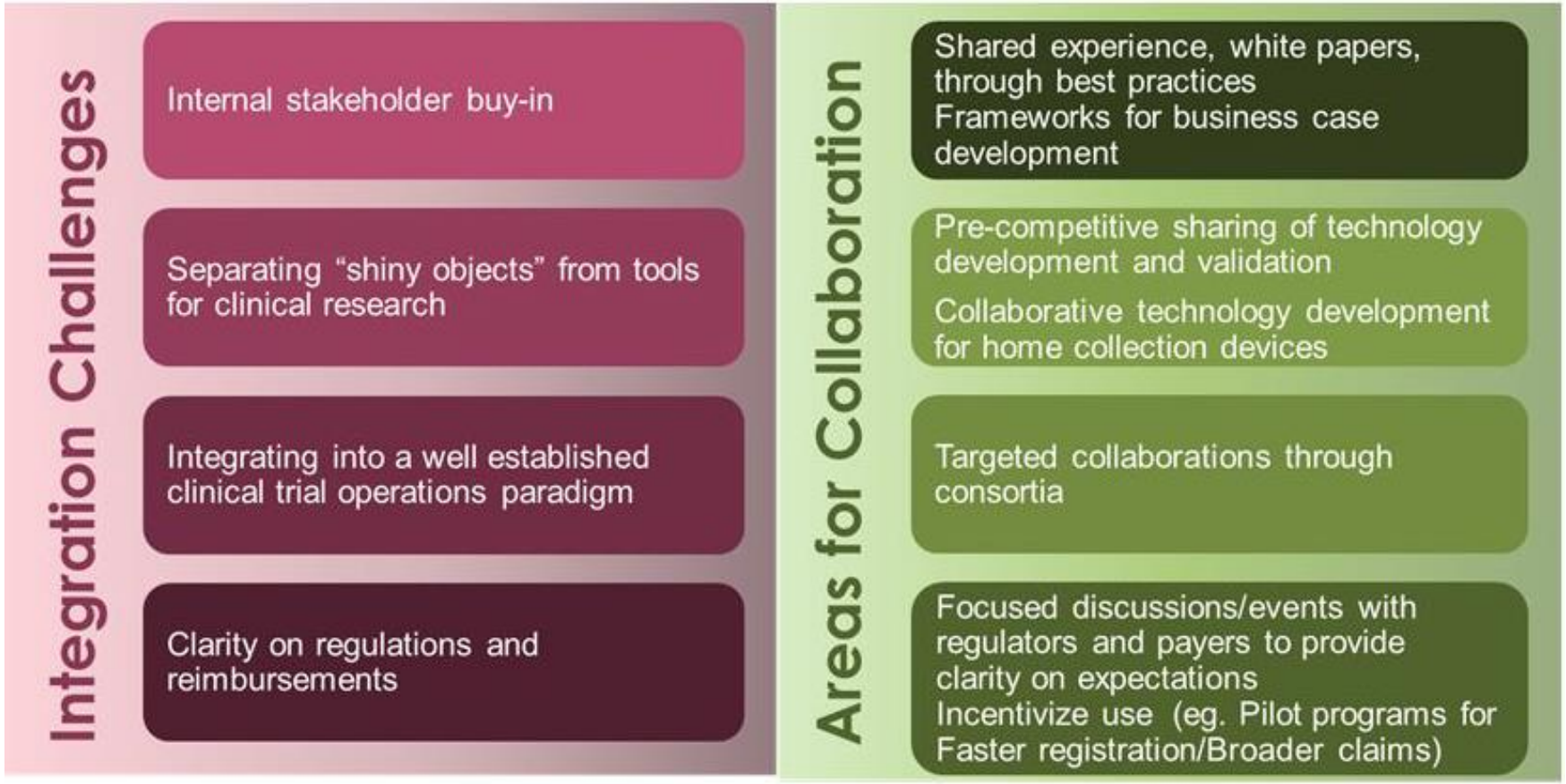
- Clinical site and Patient training – this can involve several clinical site all over the world and language translation
- Patient compliance and sample collection reliability, at home sampling needs to be a simple and straightforward as possible
- Regulatory – how are devices treated and what regulatory 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

Where can Industry, Academia and Regulators come together to Realize the Vision of Patient-Centric Trials?

Steep curve from pilot trials → routine application of "smart" approaches



Kothare PA, Jadhav PR, Gupta P, Harrelson JC, Dickmann L, *Clin Pharmacol Ther.* 2018 Apr 26. doi: 10.1002/cpt.1100.

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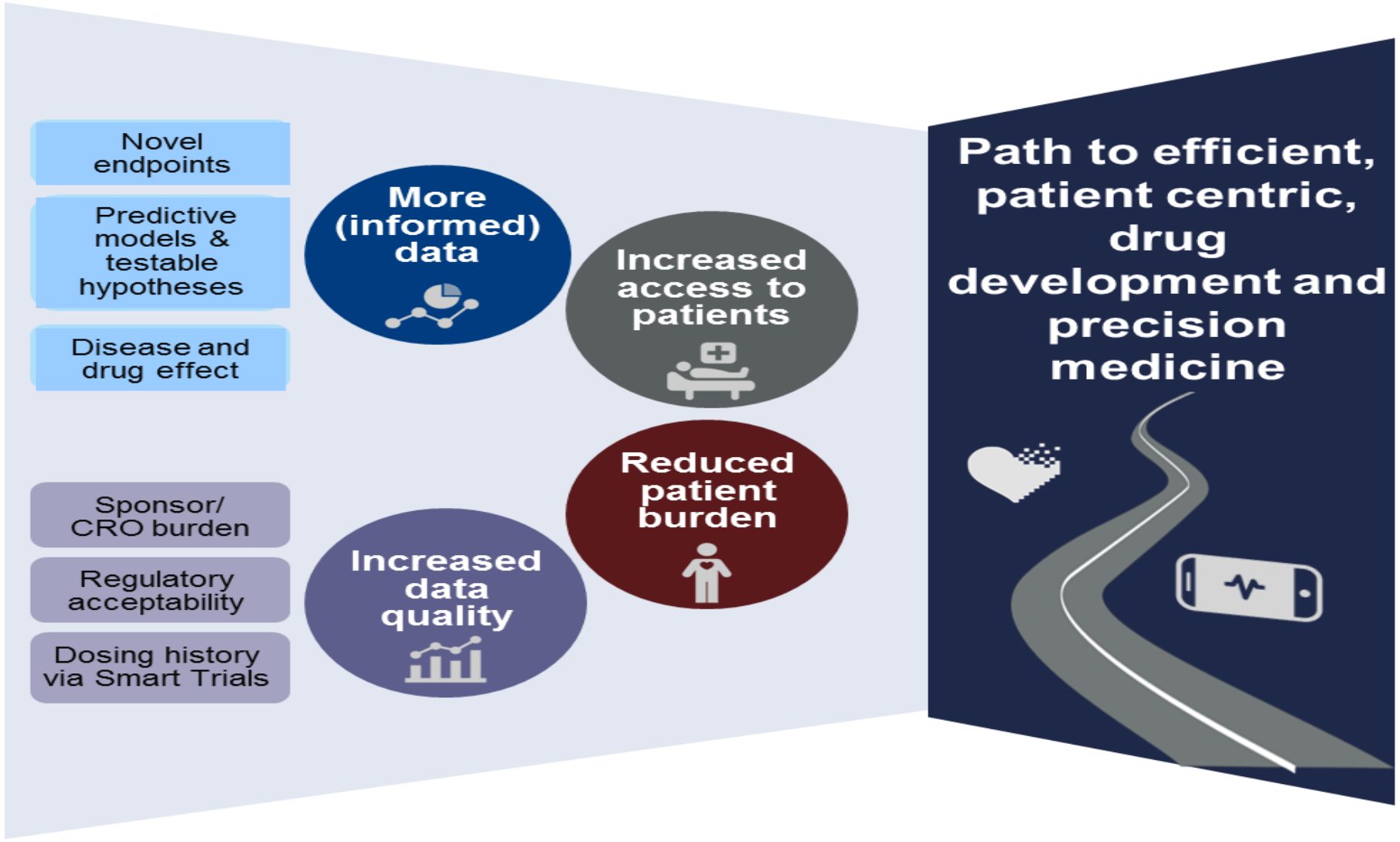
Conclusions and Future Directions

- 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

The Future!



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Acknowledgements

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

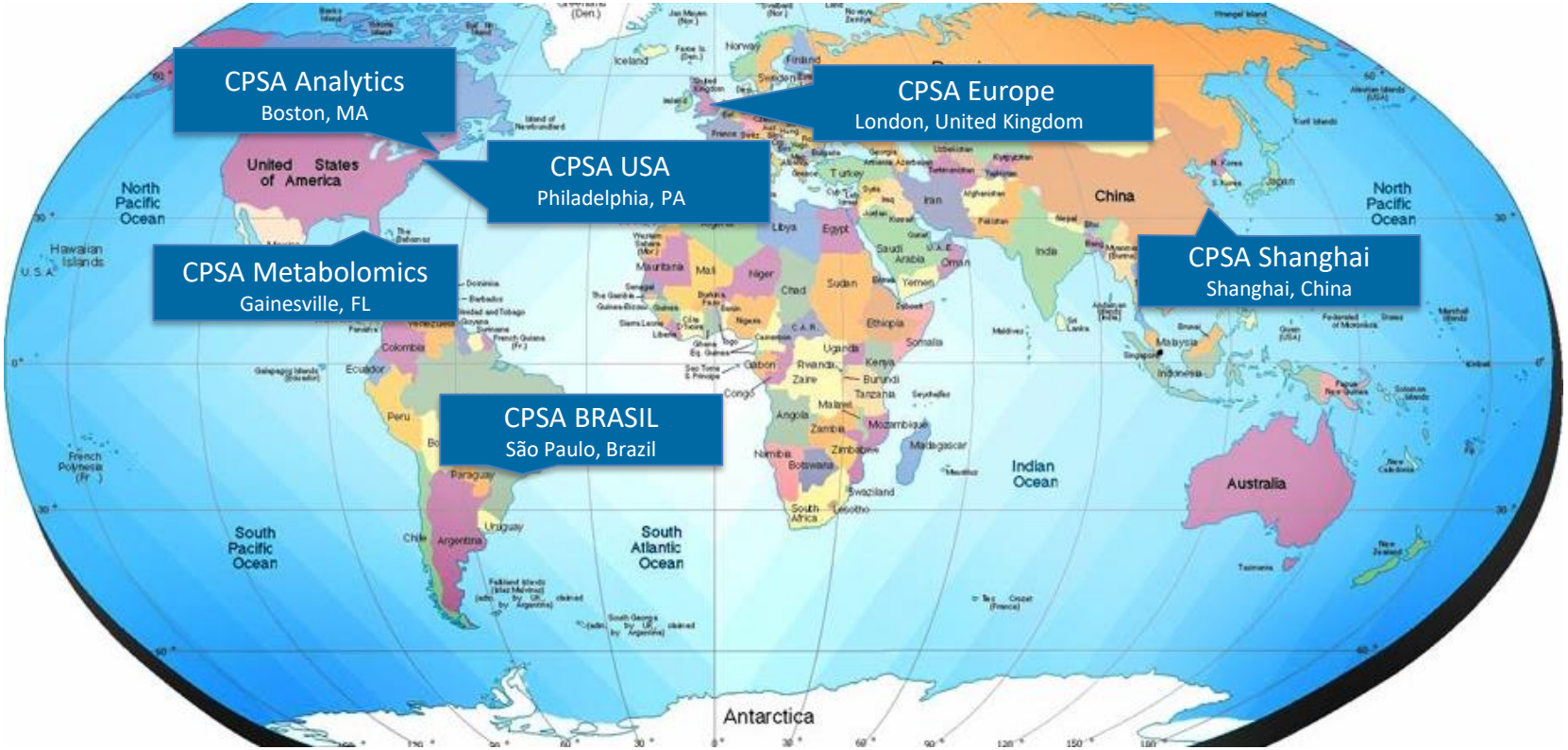
…and *many others* on the Smart Trials team

Erwin Berthier and the Tasso team

Summary & Wrap-up

Joe Siple (New Objective)

Global Community



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