PATIENT CENTRIC SAMPLING: BIONALYTICAL AND REGULATORY CONSIDERATIONS

Chiara Rospo 2 July 2023

Inspired by **patients.**
Driven by **science.**

Agenda

1. Introduction
2. Development of an innovation pathway
   - -Stages
   - -Focus on the role of bioanalysis
3. Conclusions and next challenges

Developing an Innovation Pathway: Stages of Investigation

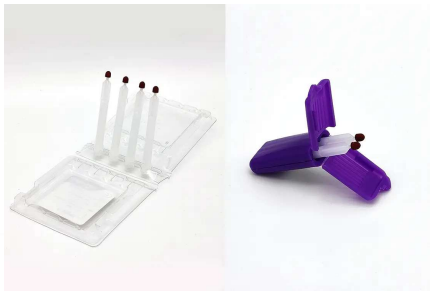
Workstream	Framing challenges and objectives	Defining criteria for solutions	Scouting Solutions
	Identifying the needs: patient`s convenience, business and scientific drive	Collection of few drop of blood near patient Define operational workflow	What is available on the market? Start of regulatory and quality considerations

Patient Centric Sampling Devices

Bioanalysis is part of the decision on device selection

- In vials - Wet Matrix
- On an absorbent VAMS® tip/pad – Dry matrix
- On filter paper – Dry Matrix



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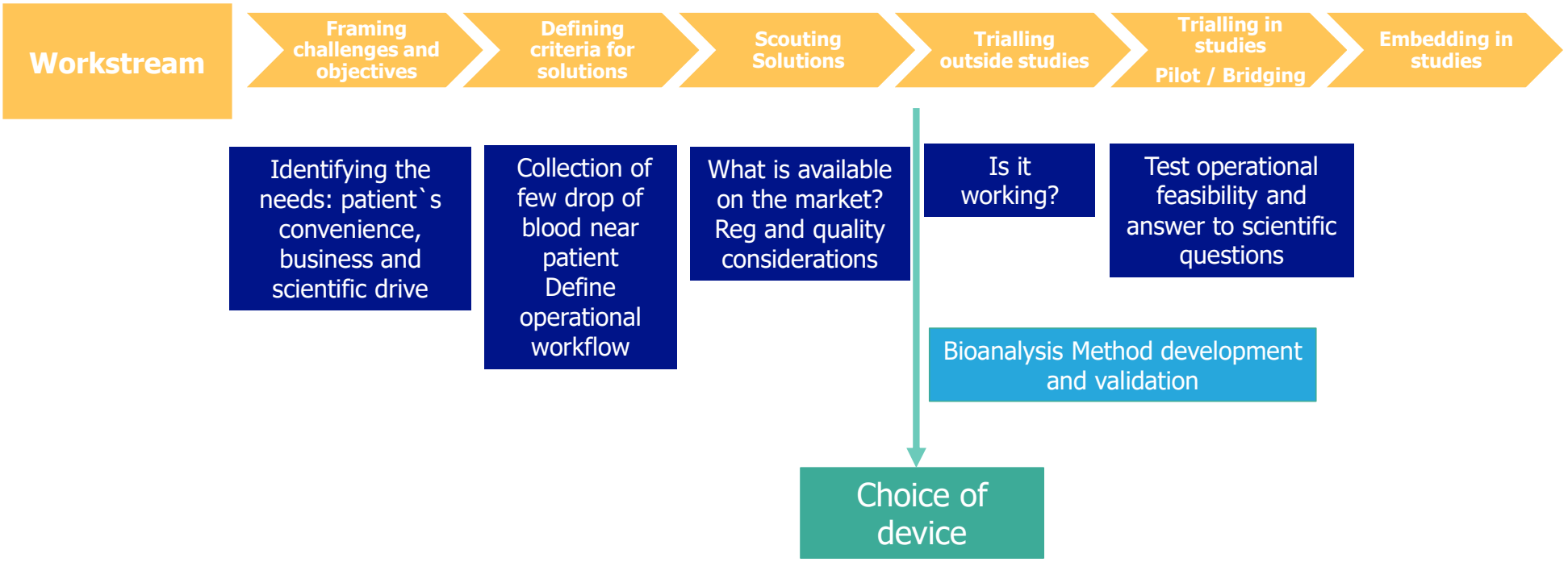
Pictures from websites of vendors

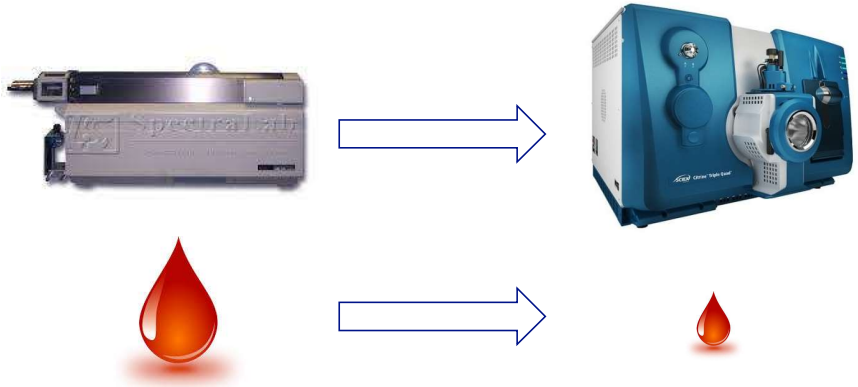
Developing an Innovation Pathway: Stages of Investigation



Bioanalytical challenges

All conventional assay validation assessment apply and there are several additional technical consideration that must be evaluated to ensure bioanalytical methods are fit for purpose

- Ensuring appropriate sensitivity can be achieved from limited volume



The requirement for greater sensitivity, selectivity, speed, and cost efficiency is driving the development of new tools such as ultrasensitive and multiplex equipment.

Bioanalytical challenges

All conventional assay validation assessment apply and there are several additional technical consideration that must be evaluated to ensure bioanalytical methods are fit for purpose:

- Stability at different storage conditions (accounting for stability during collection/transit/storage)
- Dry Matrix Samples:
  - Stability at different storage conditions (accounting for stability during collection/transit/storage: temperature, humidity, drying time, shipping conditions etc)
  - Ensure efficient extractability with sample age
  - Evaluate impact of different hematocrit: ensure same recovery at different HcT level
  - Sample homogeneity (DBS)
  - Automation compatibility
  - Presence/absence of desiccant

Bioanalytical considerations

Series of additional assessments are required with proper planning (and adequate budget assigned)

- More time to conduct additional assessments compared to traditional sampling
- Need specific bioanalytical training for the use of these devices in BioAnalytical lab
- Sample storage (especially for dry matrix samples to be stored at RT)
- Logistics
- BioAnalytical cost higher than current practices
- Bioanalytical outsourcing strategy

What are the expectations from regulators?

ICH M10 guidance **Chapter 7.6.1. Dried matrix methods (DDM)**

In addition to the typical methodological validation for LC-MS or LBA, use of DMM necessitates further validation of this sampling approach before using DMM in studies that support a regulatory application, such as:

- Haematocrit (especially for spotting of whole blood into cards)
- Sample homogeneity (especially for sub-punch of the sample on the card/device)
- Extraction of the sample from the dried matrix
- DMM sample collection for ISR: Care should be taken to ensure sufficient sample volumes or numbers of replicates are retained for ISR. Should be assessed by multiple punches of the sample or samples should be taken in duplicate

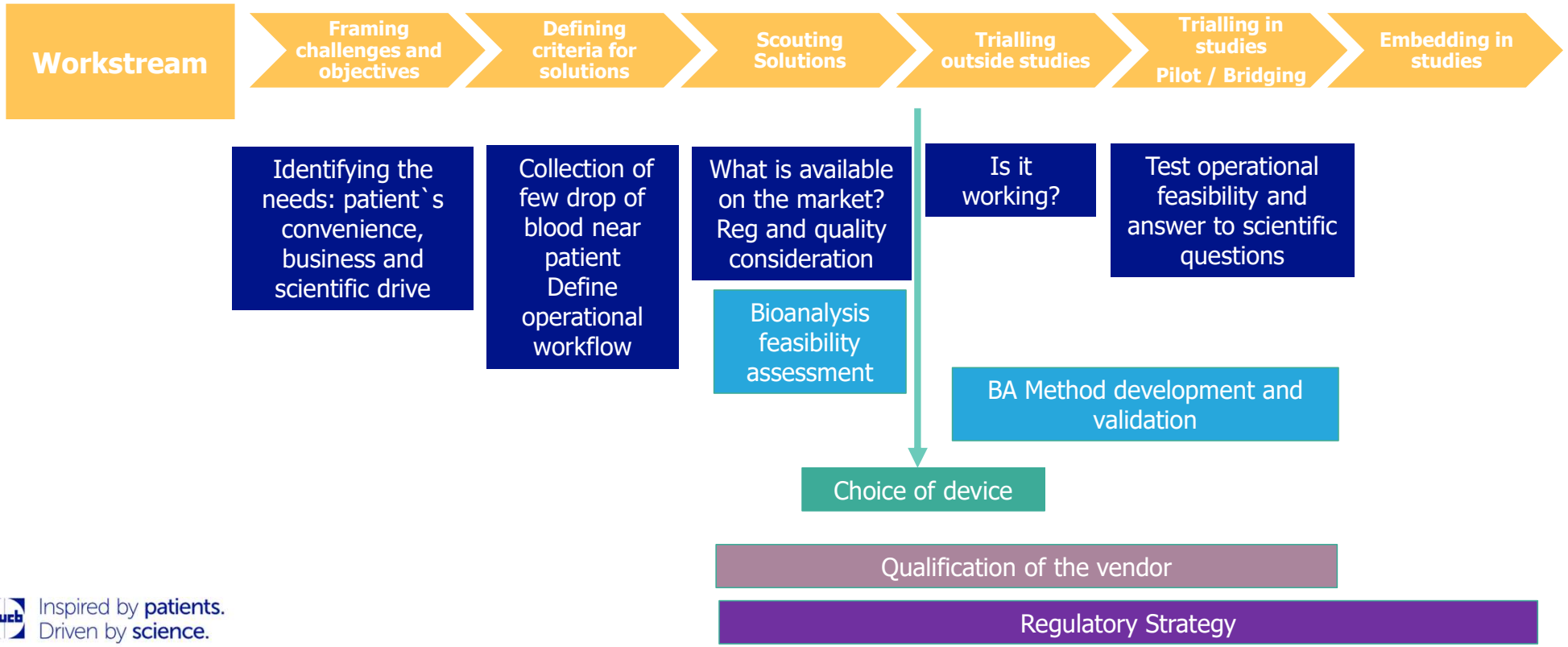
When DMM is used for clinical or nonclinical studies in addition to typical liquid approaches (e.g. liquid plasma samples) in the same studies, these two methods should be cross validated as described (refer to Section 6.2). For nonclinical TK studies, refer to Section 4.1 of ICH S3A Q&A.

Feedback from the appropriate regulatory authorities is encouraged in early drug development

https://database.ich.org/sites/default/files/M10_Guideline_Step4_2022_0524.pdf

Developing an Innovation Pathway: Stages of Investigation

- No guarantee that the device choice made is the best from a bioanalytical point of view (consideration on when to start bioanalysis).
- Bioanalysis engaged with regulatory team to set the strategy for implementation of PCS devices
- Bioanalysis engaged in the **vendor qualification** (eg shelf life, lot to lot variability, responsiveness of company)



UCB case study 1

- **Objective**: To implement the use of Mitra® for collection of blood samples for a UCB new chemical entity, and to evaluate it throughout bioanalytical assays and clinical trials.

- **Bioanalytical validation results**
  - The method was demonstrated to be sufficiently accurate, precise, and selective to reliably allow quantification of the drug candidate over the examined concentration range.
  - The method was not affected by inter-intra run variability, matrix effect, the presence of co-administered compounds, or carryover.
  - Long-term room temperature stability was proven, and negligible impact on haematocrit (between 30% and 70%) was observed.

Accuracy and precision of the drug candidate intra-run and inter-run in Mitra® (N=18)

Nominal concentration	2.0 ng/mL	6.0 ng/mL	1000 ng/mL	1600 ng/mL	2000 ng/mL
Mean intra-run precision, %CV	13.3	7.1	5.3	5.5	5.8
Mean intra-run bias, %	−7.0	0.4	1.5	1.3	3.7
Inter-run precision, %CV	13.2	6.9	5.7	5.9	6.2
Inter-run bias, %	−7.0	0.5	2.0	1.3	3.5

CV, coefficient of variation

Haematocrit effect on the drug candidate (N=6)

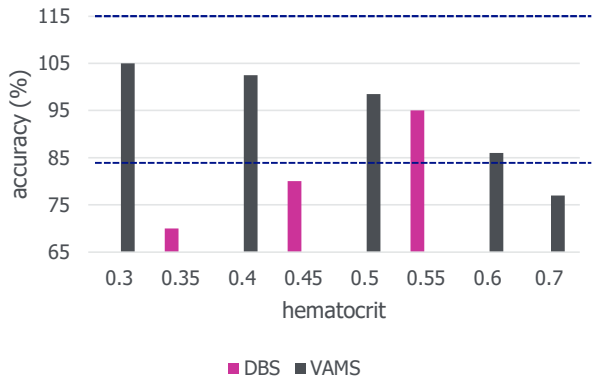
Concentration	6.0 ng/mL			1000 ng/mL			1600 ng/mL		
Haematocrit	30%	50%	70%	30%	50%	70%	30%	50%	70%
Precision, %CV	14.7	3.5	9.1	7.1	9.3	4.5	4.1	6.6	6.5
Bias, %	15.3	9.5	7.5	3.0	6.0	3.0	3.1	5.0	5.0

CV, coefficient of variation

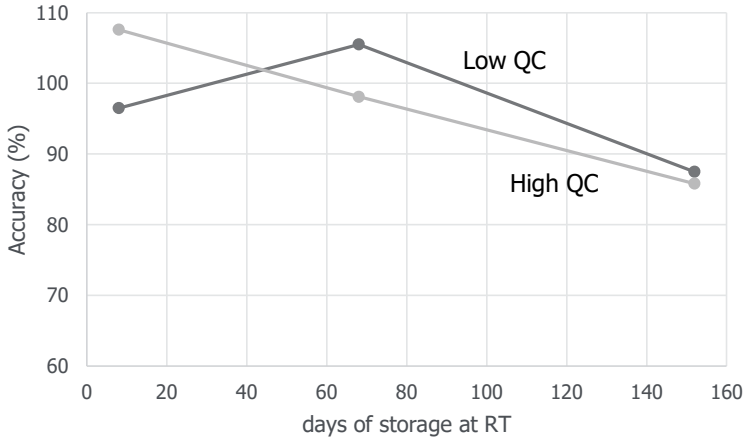
Source EUFEMED 2019 poster

Haematocrit and stability assessment examples Case Study 2 and 3 and 4

- Case Study 2: When Haematocrit drives the decision on which device to use
- Case Study 3: When stability (or extraction efficiency) drives the operations of sample shipment frequency and analysis
- Case Study 4: When stability of metabolites (interconversion at RT, light sensitive) drives the choice not to implement PCS devices and use conventional blood sampling



Case Study 2



Case Study 3

Operational considerations impacting bioanalysis

Good bioanalytical quality data starts with good <u>quality</u> (sample integrity) and <u>quantity</u> of samples received at the bioanalytical lab

- Procedure of sample collection, handling, storage and shipments are paramount to get samples at bioanalytical lab that can be analysed.

Patient receives kit containing all the supplies for sample collection and instructions

Patient/Caregiver collects samples

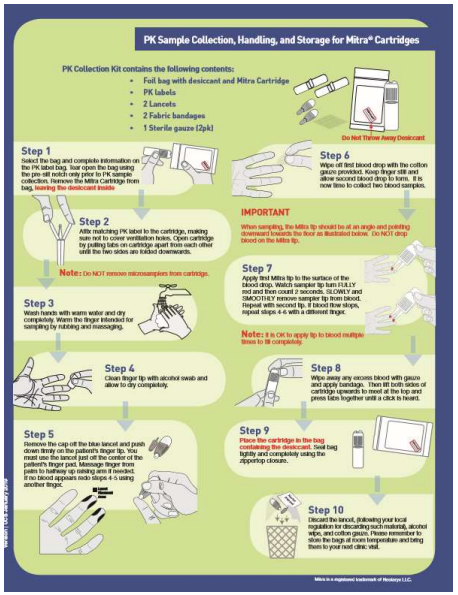
Patient/Caregiver returns sample (post/next site visit)

Lab receives sample and perform bioanalyses

Operational considerations impacting bioanalysis

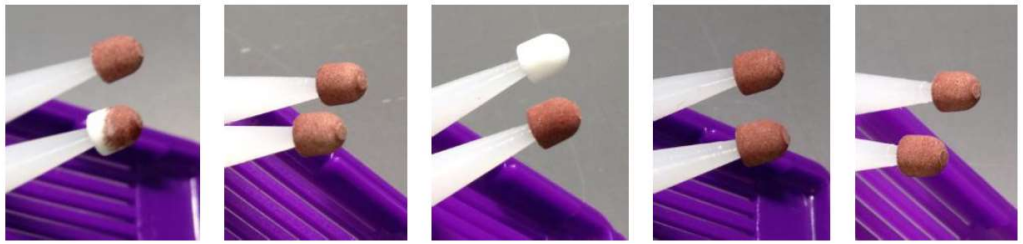
Good bioanalytical quality data starts with good <u>quality</u> (sample integrity) and <u>quantity</u> of samples received at the bioanalytical lab

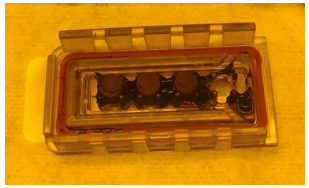
- Collection, shipment procedures designed in collaboration with bioanalysis:
  - Brochures/Videos for Patients/Care givers, Clinical Staff, Central lab (if involved)
  - Study Operations Manual
  - Investigator Meeting Presentations

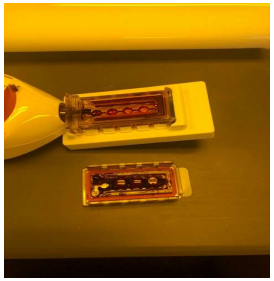


Operational considerations impacting bioanalysis

From theory to practice



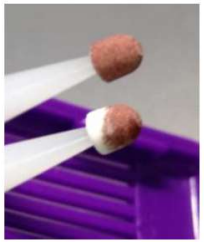




Suppression of signal in LCMS MS indicating matrix effect
potential causes:
-Skin not clean, with cream..
-Storage of samples at home

Mitigations

- **On time feedback from participants/caregiver and from bioanalytical CRO** after visual inspection of samples received to Clin Ops is important for the success of the study
  - Redesign of instructions
  - Retraining

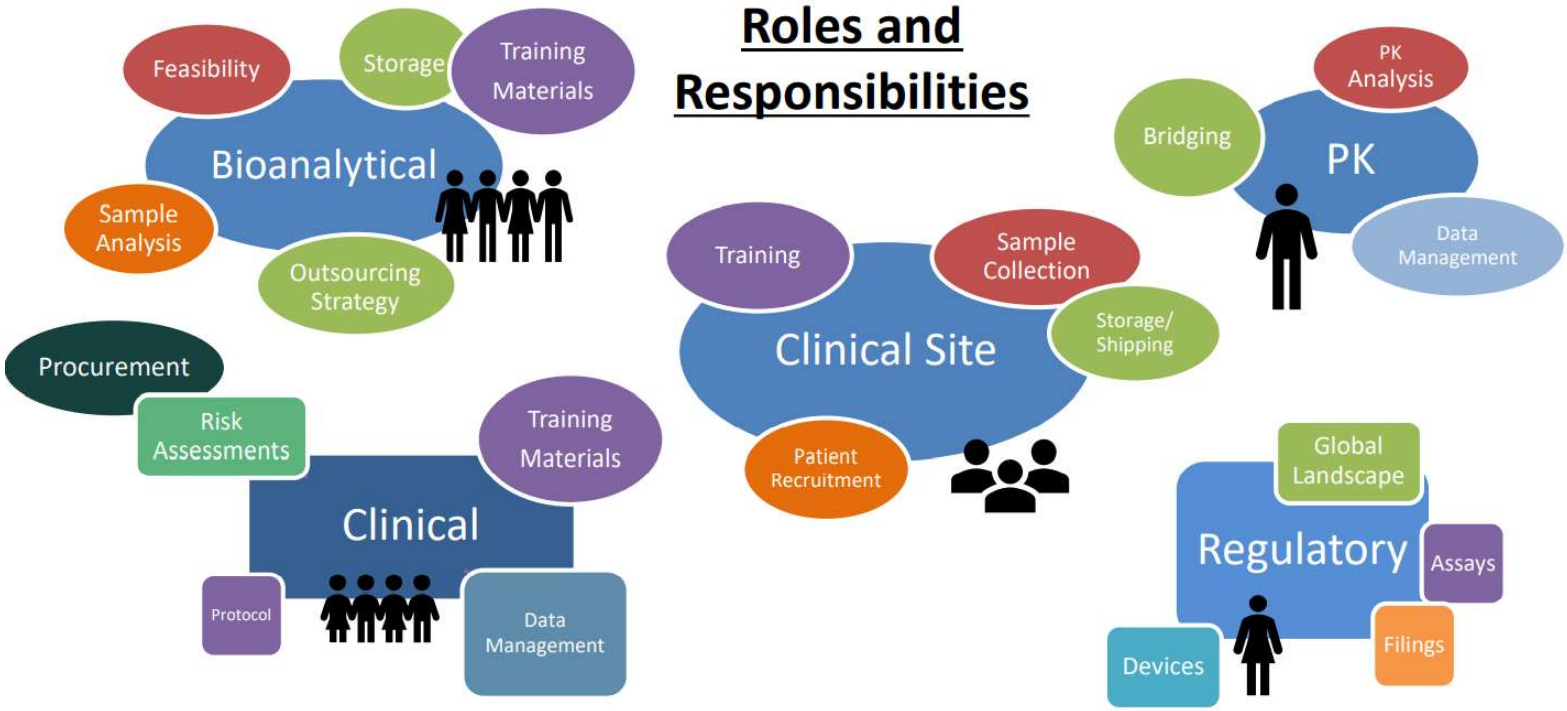


Massage the finger from palm to hallway up raising the arm

To avoid sample contamination

Store the foil bags at room temperature in the study backpack protected from light prior shipment

Implementation pathway: common journey



Conclusions

- Bioanalysis is a partner in the journey for implementation of patient centric sampling solutions.
  - The sooner the journey start the higher is the chance to mitigate the issues and overcome hurdles
  - Ensure adequate budget and time
- The awareness of their benefits and the common effort that will be made by all the stakeholders in the drug development process towards a human centric health care approach will be detrimental to overcome the actual challenges for their implementation.

Patient Centric Sampling Interest Group

IQ CPLG/TALG Patient Centric Sampling (PCS) Working Group

European Bioanalysis Forum

https://www.pcsig.org/
https://iqconsortium.org/

https://e-b-f.eu/
https://www.imi.europa.eu/get-involved/patients

What`s next?

- Evolution of device sampling technologies:
  - Enabling date and time stamp of sample collection and traceability
  - Embedded temperature monitoring
  - Volume
  - Collection of other matrices
- Regulatory acceptance
- Expand the use of these devices for other endpoints rather than PK:
  - Vaccine research (viral load testing, track protection)
  - Epidemiological studies/longitudinal studies (Biomarker)
  - Biochemistry safety panel
- Organisational acceptance (DCT model)
- Acceptance by society (PCS as `new norm`)

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