PK studies in Infants & Children:

Are Dried Blood Spots the answer?

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The Issue: Age Appropriate Dosing

- Drug dosing in children based on scaling adult dosing data according to weight, BSA or BMI

- Approach does not take into account physiological differences between infants, children, adolescents and adults (e.g. 'ADME', disease processes) and so dosing regimen may be inappropriate

Many important drugs not licensed or without PK data
e.g. Corticosteroids, ACE inhibitors

The Problem: Performing PK Studies

PK studies in children beset with ethical and technical challenges.

PK studies in children require

(i) Relatively large volumes of blood
(ii) Repeated vene-puncture to obtain blood

Together (i) & (ii) are generally unacceptable to parents, researchers and ethics committees

'POP-PK' modelling techniques partly resolve the issue of obtaining multiple samples from patients for PK studies

EMA Guidelines

- Guideline in term and preterm neonates*:- 'Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1 % at any single time'
  - The total volume of blood is estimated at 80 to 90 ml/kg body weight
  - 3 % corresponds to about 2.4 to 2.7 ml blood per kg body weight
  - Remains maximum in the case of simultaneous trials
- Guidelines are applicable to infants and children
- Deviations from these recommendations must be justified to the relevant ethics committee

*Doc. Ref. EMA/536810/2008

DBS - The Solution ?

DBS sampling has the potential to overcome many of the practical and ethical issues surrounding blood sampling in children. However, DBS methodology *lacks validation* in the clinical arena.

Unknowns

1. Can sampling methods established for neonatal screening programs be adapted to suit the more rigorous sample collection methods required for drug dosing studies in children ?

2. Will children, parents and healthcare professionals find the demands of DBS sampling for drug studies acceptable?

3. If 1 & 2 overcome, does introduction of DBS technology increase the feasibility of performing drug dosing studies in children?

The ‘CUBS’ STUDY

(Caffeine Using Blood Spots)

An ‘in field’ assessment of ‘Dried Blood Spot Methodology’: Determination of caffeine pharmacokinetics in infants

Collaboration between
•University Hospitals of Leicester NHS Trust
•University of Leicester
•GSK

University of Leicester

gsk GlaxoSmithKline

Why preterm babies and why caffeine?

1. If DBS + PK modelling “works” in most vulnerable age group then it should work for all
2. Caffeine commonly used drug in neonates
3. “In –house” DBS method available
4. PK for caffeine known
5. Potential Long Term Study: Px with fixed dose caffeine or to a plasma level ?

Outcome Measures for Study

(A) Bedside Outcomes

(i) Time taken by Operator
(ii) Success rate: to get blood, apply blood properly, N^{os} of spots per patient
(iii) Parent and Operator acceptability

(B) Laboratory Outcomes

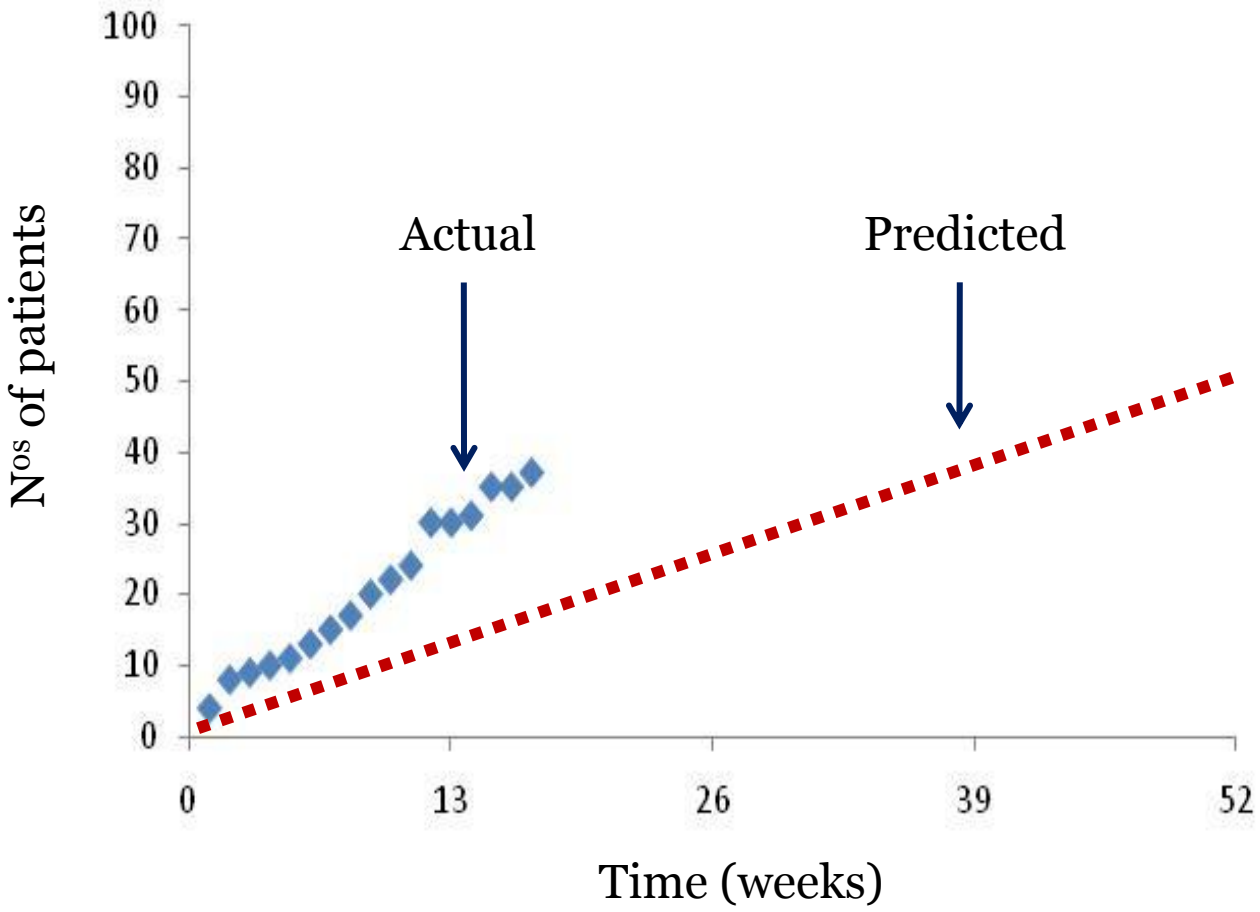
(i) N^{os} Spoiled samples, missing data points
(ii) Precision, accuracy, robustness

(C) Overall Outcomes

(i) Compare DBS – POP PK data for caffeine with published data
(ii) Blood volume within EMA guidelines

Patient Recruitment Jan 2010 to date

(Initial Target N = 50)



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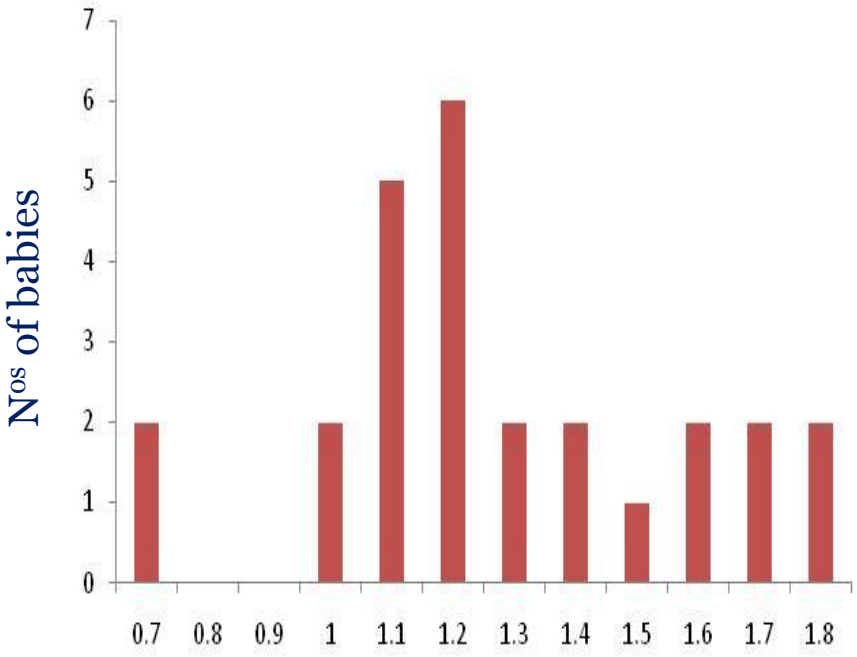
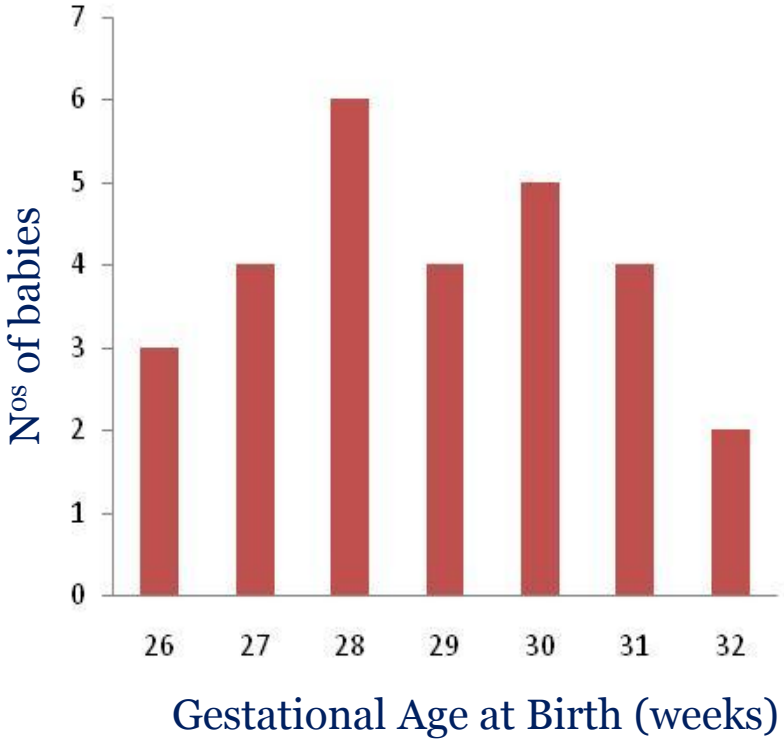
Patient Demographics





N= 36

Birth weight Range = 0.73 to 1.84 kg

Gestational Age = 26^{+3} to 32^{+1} weeks

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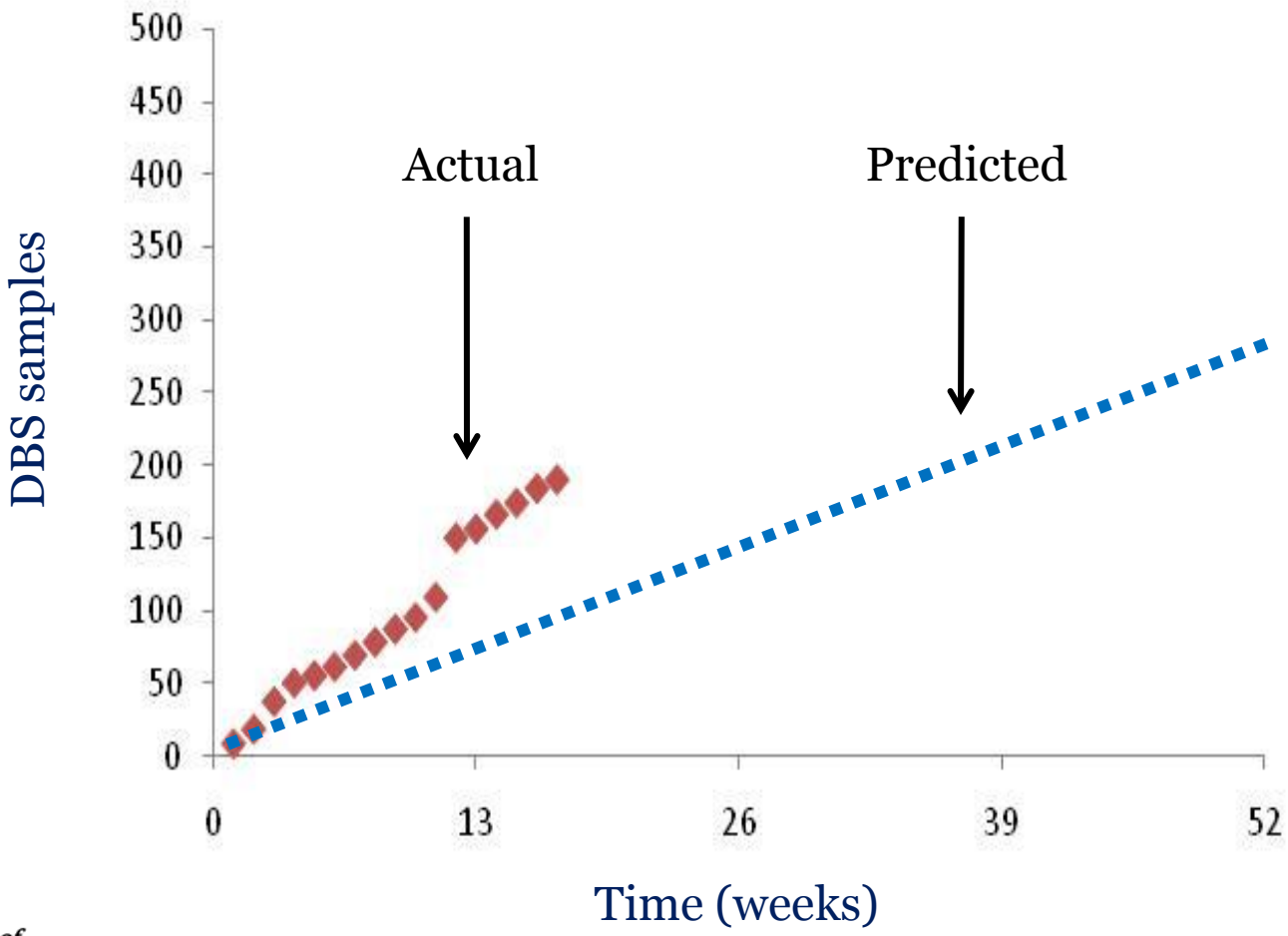
Accrual of DBS samples

(Target N = 250 to develop 'Pop-PK' model)



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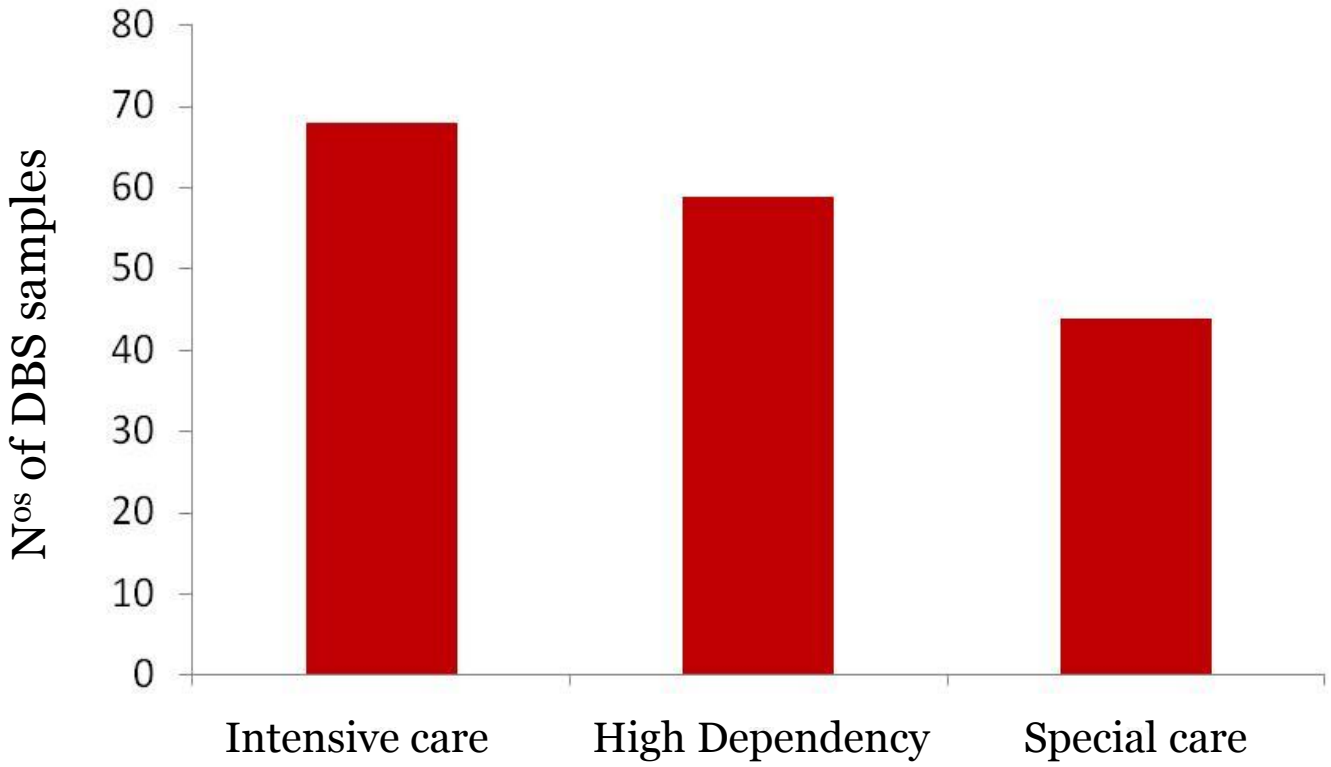
DBS sampling and Patient Dependency



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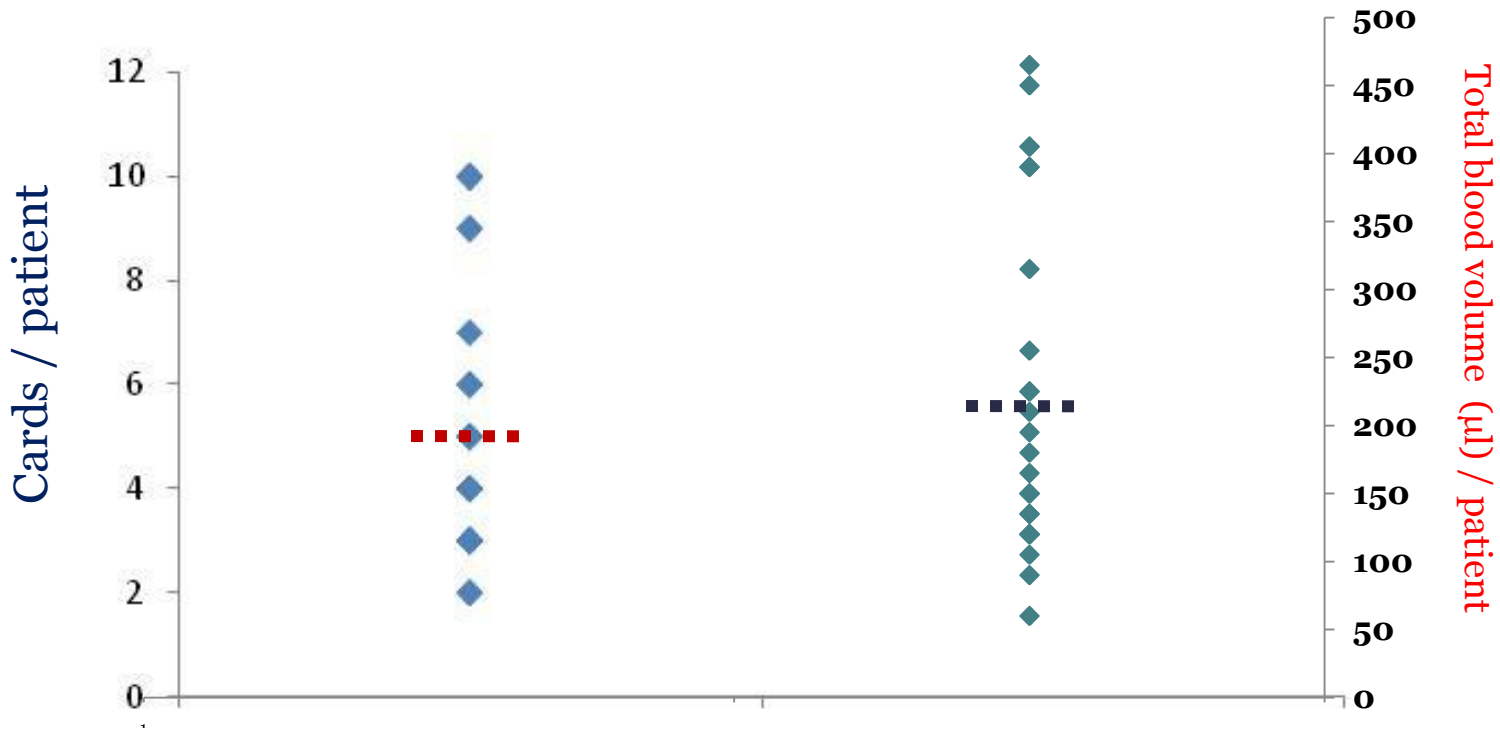
Nos of cards & Total Blood Volume

Mode Nos Spots / Card = 2

N = 36



Mean Nos cards/ patient = 5

Mean blood volume /patient = 220 µl

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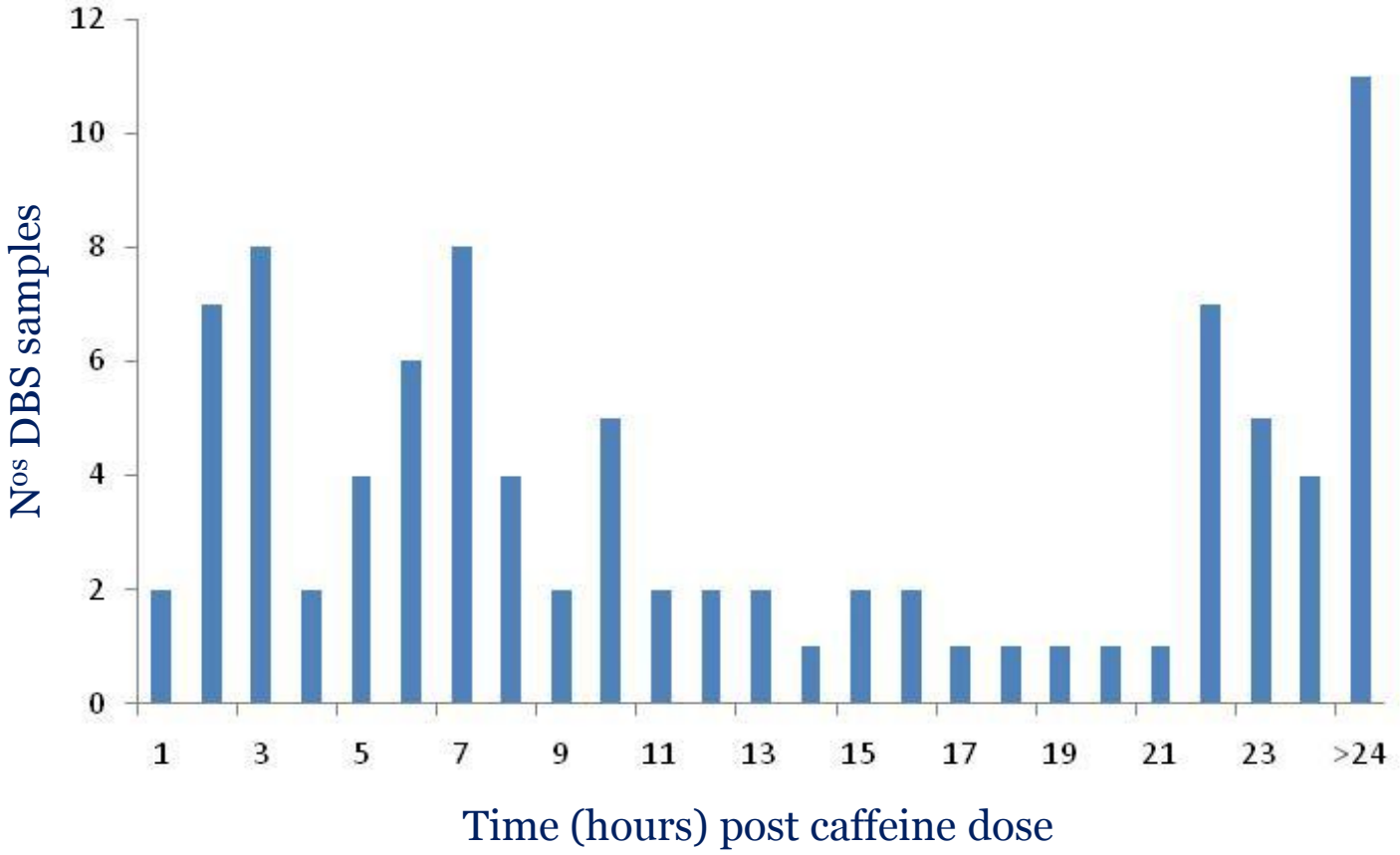
DBS Sampling Profile

(Post Caffeine dosing)



>24 hrs refers to DBS samples obtained after stopping caffeine therapy

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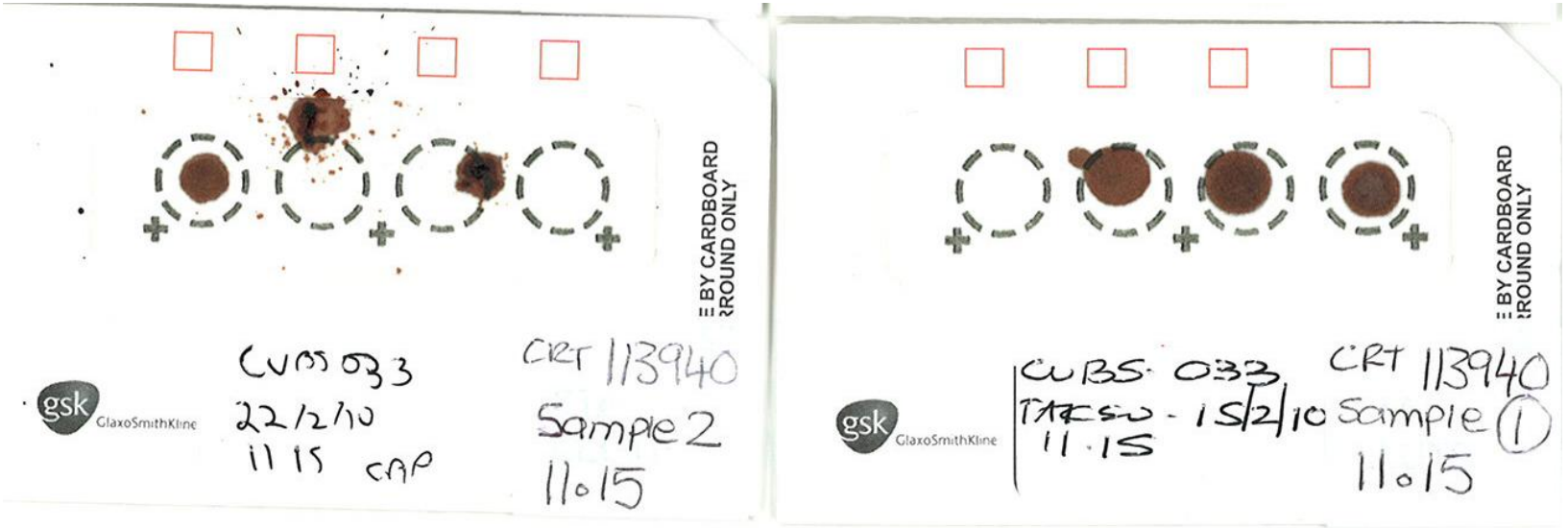
Sampling Issues



Preliminary Conclusions

- Accrual of patients and DBS cards above expectations
- Blood volume using DBS comfortably within EMA guidelines
- DBS Sampling in high 'dependency' possible (maybe easier)
- Important to monitor DBS sampling times and methods
- Partnerships between academia and industry are essential and necessary for this work

The 'CUBS' Study Group

Babies, Parents, Nursing & Medical Staff, NNU LRI

Leicester Group

- David Field
- Elaine Boyle
- Venkatesh Kairamkonda

- Hussain Mulla

- Carmen Soto
- Parul Patel

- Rekha Patel

GSK Group

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Questions?

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