Midazolam Measurement and Modelling using Matrix Samplers (The 4M's Study)

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Importance of getting the dose right

"To ensure that drug efficacy is optimised for *every age category* and……

….ensure that dose selection is associated with an *acceptable safety margin across the predicted range of drug exposures*"

Background

Unlicensed and off label use of medicines in children very common

European examples of unlicensed and off label prescribing for children

Reference	Prescribing site	Unlicensed (%)	Off label (%)	Unlicensed and off label (%)
t'Jong *et al*[7]	ICUs	54.0	17.8	71.8
Conroy *et al*[5]	Wards	7.0	39.0	46.0
Chalumeau *et al*[9]	Outpatients	4.0	29.0	33.0
McIntyre *et al*[10]	General practice	0.3	10.5	10.8

ICUs, intensive care units.

Risks: (i) Reduced Efficacy (ii) Toxicity

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P Hill ; Off licence and off label prescribing in children: litigation fears for physicians, Arch Dis Child 2005;90(Suppl I):i17–i18. doi: 10.1136/adc.2004.058867

Why is data on drug dosing in children so poor?

Lack of Engagement by Pharmaceutical Industry

- Economics
- Too difficult

↓

Left to Paediatricians
=> “guesstimate” correct doses

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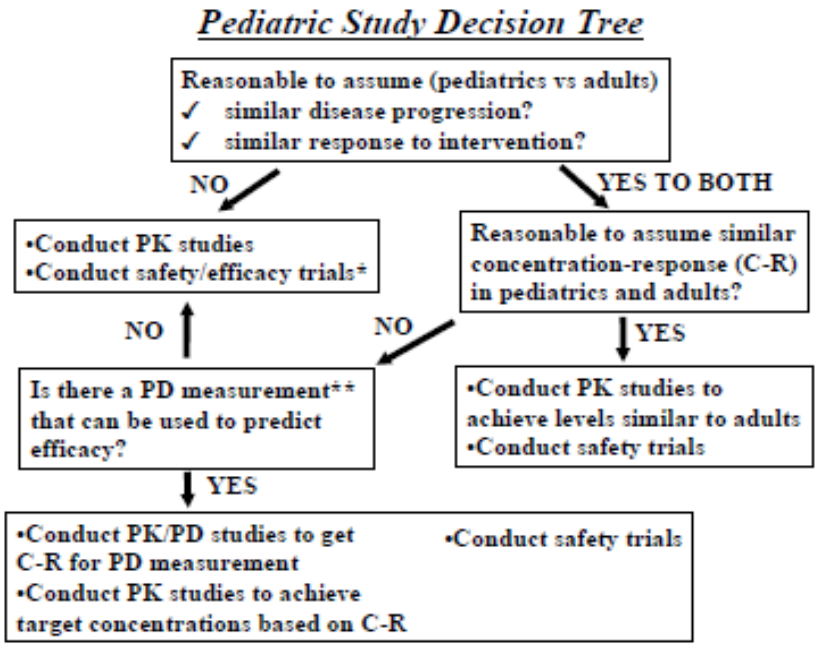
PK-PD studies & Drug licensing

Disease only occurs in children



Similar disease process in adults & children

Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

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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

- ‘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’ *
- Deviations from these recommendations must be justified
  - In neonates the total volume of blood is estimated at 80 to 90 ml/kg body weight
  - 3 % corresponds to 2.4 to 2.7 ml blood per kg body weight

Doc. Ref. EMEA/536810/2008

PK studies in Infants & Children: Is DBS the answer?

- DBS sampling : Potential to overcome many of the practical and ethical issues surrounding blood sampling in children.
- 'CUBS' Study: Caffeine PK study in neonates using DBS Methodology

Main issues

- High proportion of spoilt samples
- Haematocrit bias

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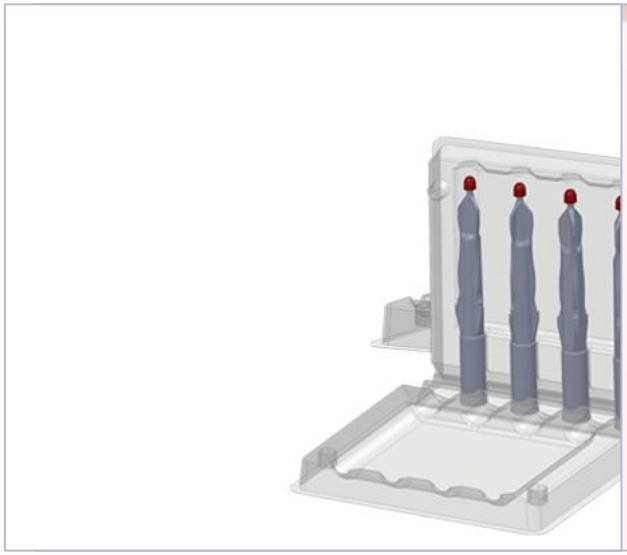
VAMS tips and 4Ms study



The 4Ms Study: Why Midazolam ?

- Used in children => ICU and peri-operatively
  - sedative, anxiolytic & amnesic agent
- Side effects => cardio-respiratory depression, withdrawal symptoms => Increased morbidity and mortality

Have we got the dose of Midazolam right for children ?

**Ince et al => Suggests critical illness alters Midazolam PK*
? Due to SIRS

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*Ince I, de Wildt SN, Peeters MYM, et al. Critical illness is a major determinant of midazolam clearance in children aged 1 month to 17 years. Ther Drug Monit 2012; 34:381–9

Study Hypotheses

1. *Critical illness alters midazolam PK*

2. *In children administered IV drug VAMS tips and traditional wet samples provide equivalent blood Midazolam and 1-OH Midazolam (active metabolite) concentration measurements*

Patient Population and Blood Sampling

- Children between 1 month and 16 years, administered IV Midazolam (Bolus dose +/- Continuous infusion)

- Blood Sampling:

    1. *Opportunistic samples: Extra blood collected when sampling blood for routine clinical tests*
    2. *Scavenged samples: Blood collected for routine clinical laboratory tests but no longer needed*
    3. *An extra blood sample for research purposes*

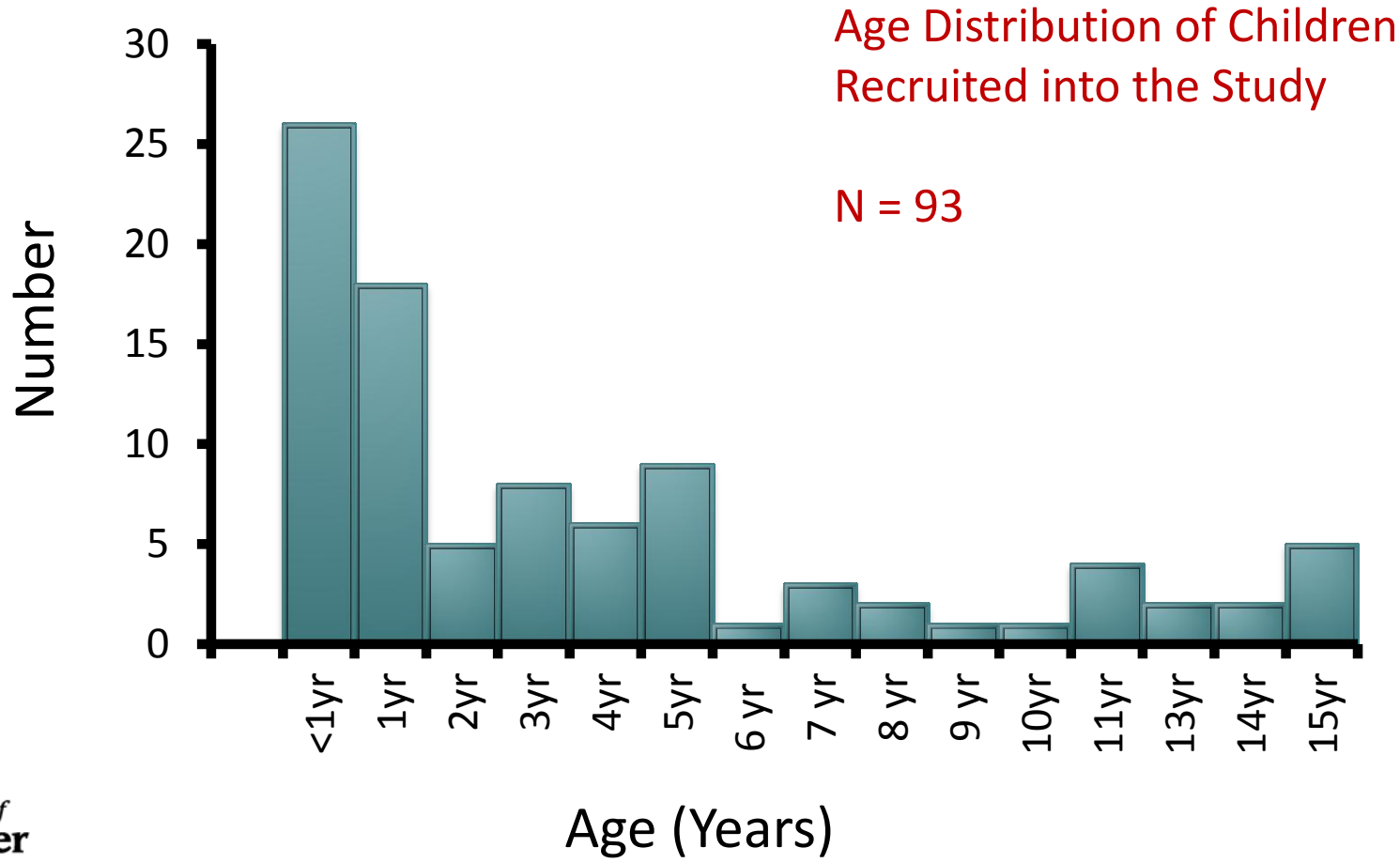
    All blood collected in EDTA tubes prior to adsorption onto VAMS tips

    Blood adsorbed onto 3 different VAMS tips for each PK time point

Study Blood Sample Management

- VAMS tips stored in bespoke cartridges containing desiccants at room temperature
- Wet blood samples stored in dedicated study freezer at -20^{o} C
- Samples stored on clinical site for up to 90 days prior to assay at GSK laboratories (Ware, UK)
- Blood midazolam and 1-OH Midazolam concentrations are analysed by HPLC / MS

Data: April 2015 - Sept 2016



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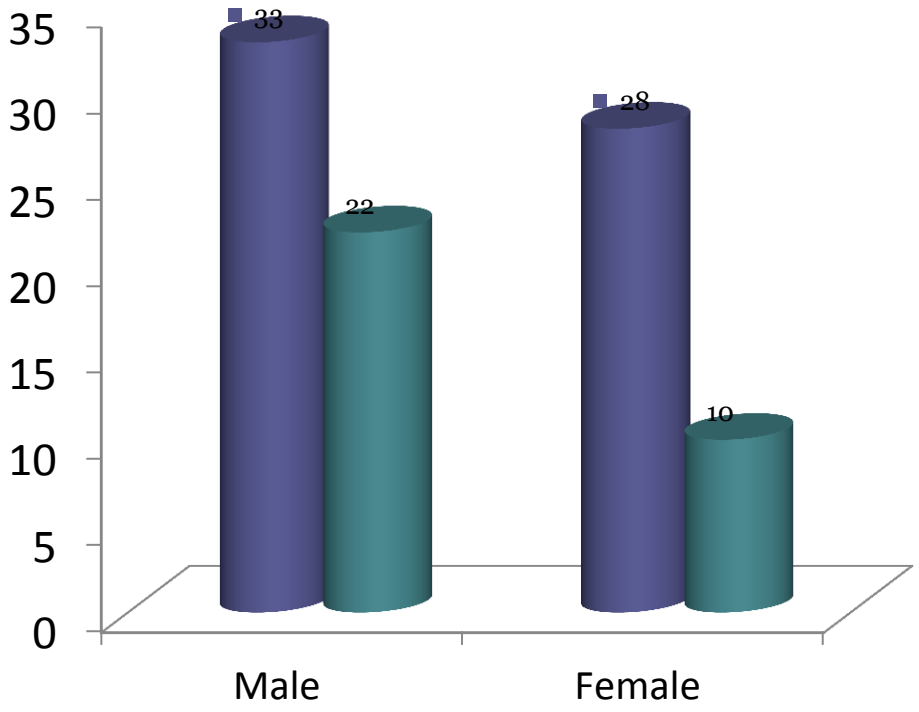
Data: April 2015 - Sept 2016



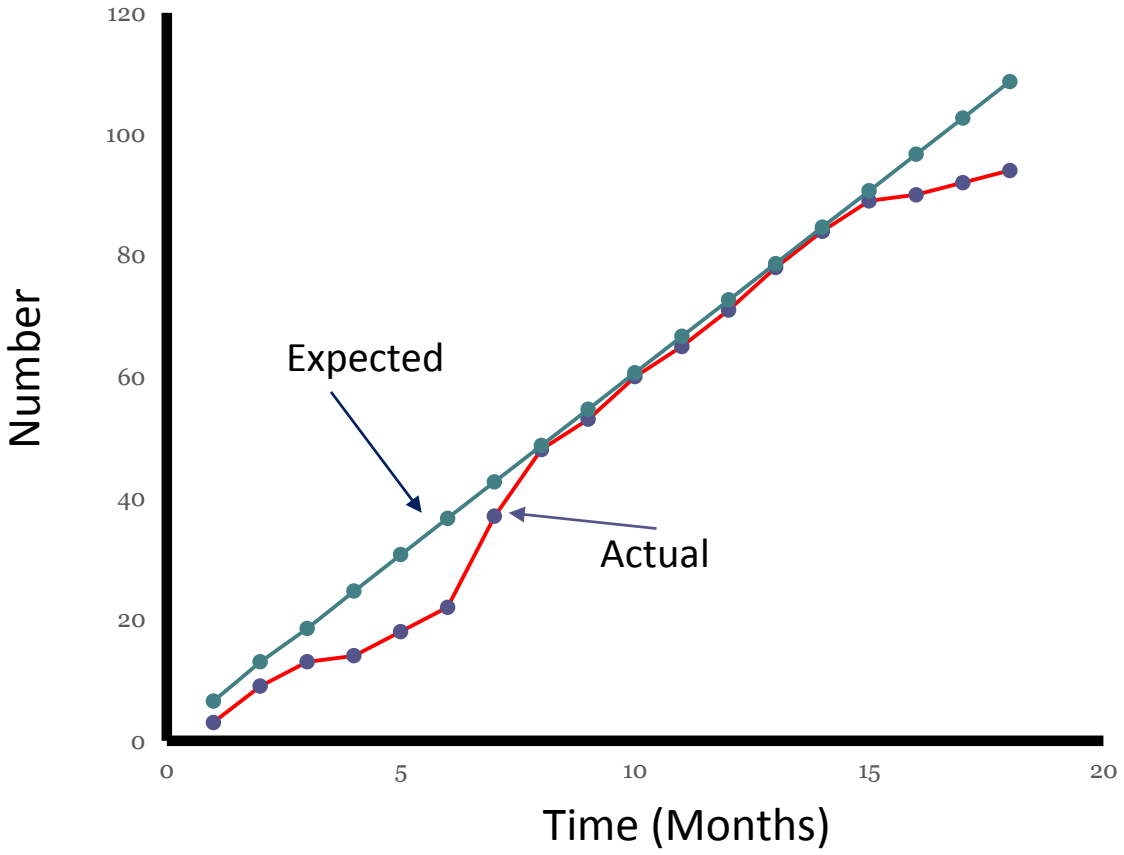
Gender Distribution & Illness Severity of Children Recruited into the Study

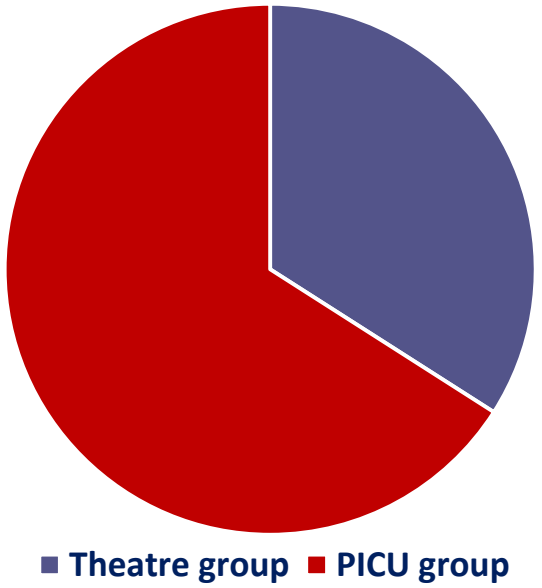
N = 93

PICU Group 61

ES Group 32

Recruitment & Illness Severity





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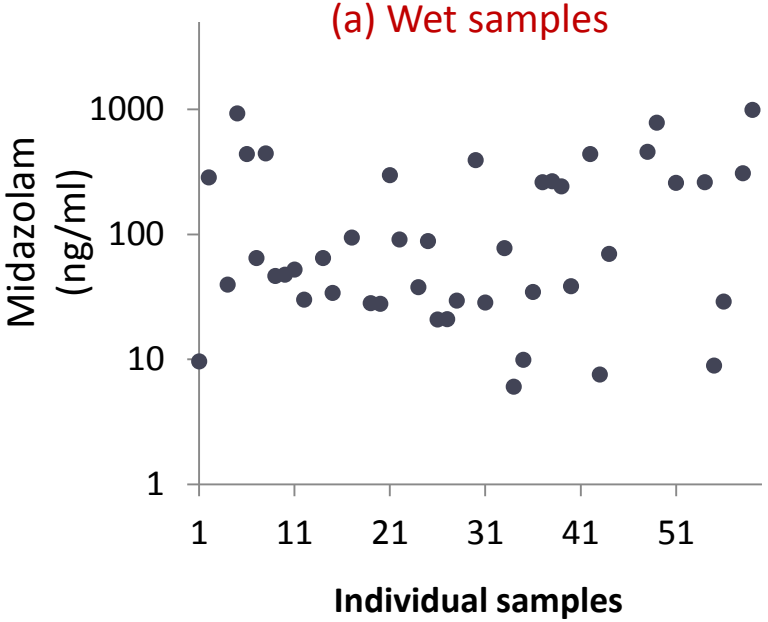
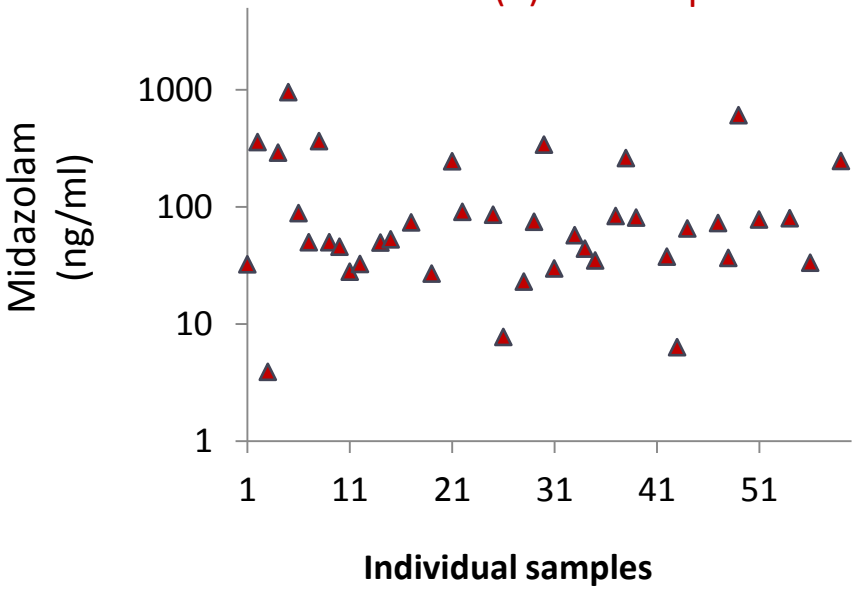
Midazolam concentrations in patients

N = 56 patients, *N* = 199 time points

(a) Wet samples



(b) VAMS tips



	PICU Group	ES Group
Mean Midazolam Concentration (ng/ml)	322	28
Range Midazolam Concentration (ng/ml)	5 - 1987	5 - 161

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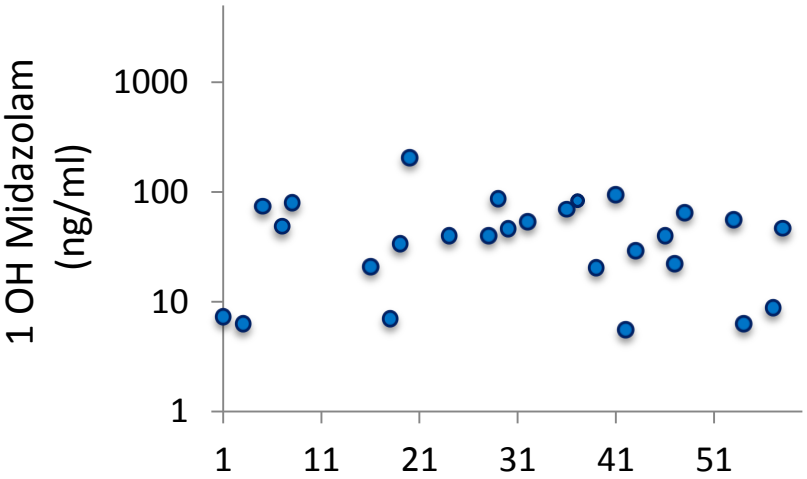
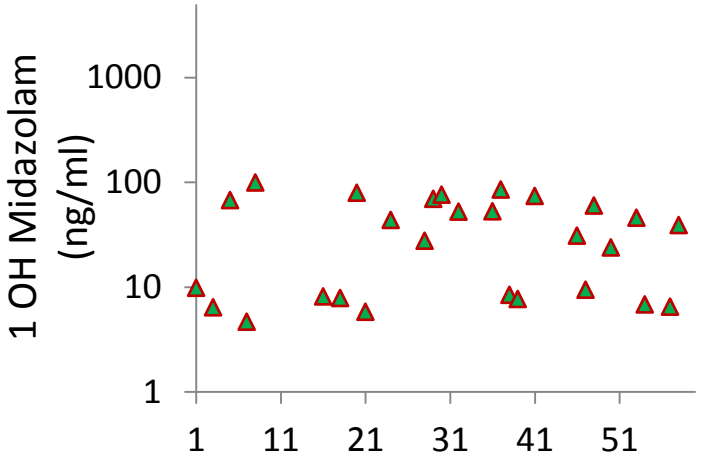
1-OH Midazolam concentrations in patients

N = 56 patients, *N* = 199 time points

(a) Wet samples



(b) VAMS tips



	PICU Group	ES Group
Mean 1-OH Midazolam Concentration (ng/ml)	42	6.6
Range 1-OH Midazolam Concentration (ng/ml)	5 - 211	5 - 8

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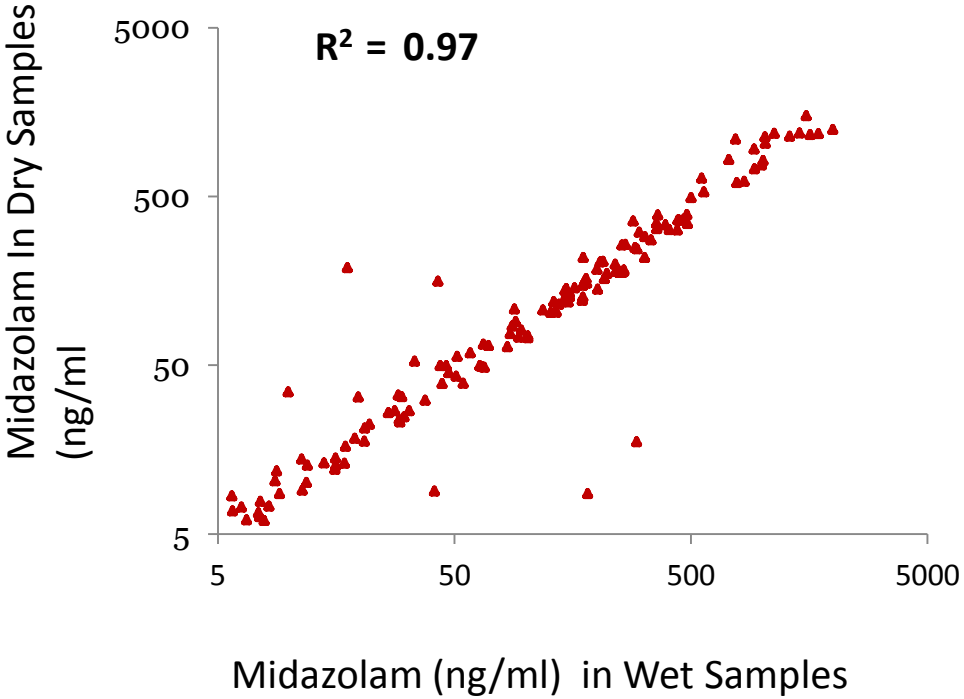
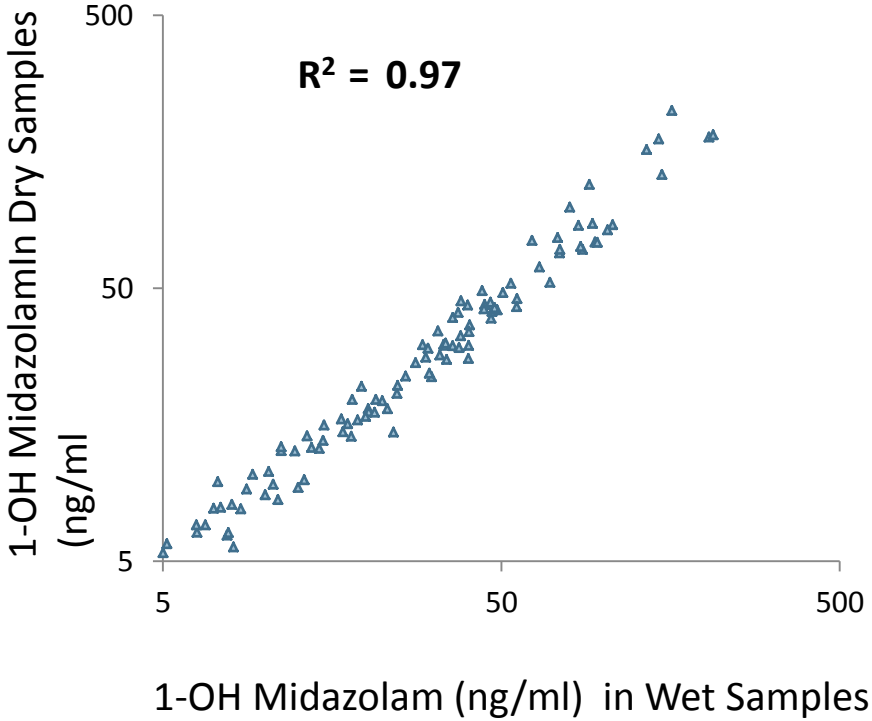
Relationship between (a) Midazolam and (b) 1-OH Midazolam concentrations determined from wet blood samples and dry samples

N = 56 patients, *N* = 199 time points





Preliminary Findings

- *Collecting blood samples for PK studies onto VAMS tips is simple*
- *Training to collect blood onto VAMS tips can be achieved in a relatively short period of time*
- *Management and storage of VAMS tips is easier than for wet samples*
- *Spoilt VAMS tips were uncommon (unlike dried blood spots)*
- *There is a strong correlation in blood midazolam and metabolite concentrations comparing VAMS samples and wet samples*

Conclusion

- VAMS tips are superior to dry blood spots in relation to spoilt samples
- Our initial analysis suggest that VAMS tips provide equivalent concentration data to wet samples

The ‘4Ms’ Study: Key Collaborators

Sponsor : University of Leicester
Funder: Neoteryx Limited
GSK

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Neoteryx
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University Hospitals of Leicester NHS
NHS Trust

gsk GlaxoSmithKline

Thank You

Any Questions?