Neonatal abstinence – not just a problem for the neonatal period

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SACCH Conference 18th March, 2016
Outline

- background
- management
- short term associated features
- longer term
Neonatal Abstinence

“a withdrawal syndrome of infants, caused by cessation of the administration of licit or illicit drugs”

Which drugs?

- opioids
- benzodiazepines
- SSRI
- caffeine/nicotine
- stimulants (?)
  - cocaine
  - amphetamines
- cannabis (?)
- alcohol (?)
Epidemiology

- substance misuse in pregnancy
  - 4 – 5%
  - probably falling in the UK
  - mums getting older
- neonatal abstinence
  - 3 – 4 per 1000 live births
  - under recognised and under reported
  - differences in management
- alcohol a major confounder

Kreitinger C, Gutierrez H, Hamidovic A et al. Pharmacotherapy 2013
McGlone L, Mactier H, Hassan H, Cooper G. Arch Dis Child 2013
Percentage of positive results using each technique

<table>
<thead>
<tr>
<th>Substance</th>
<th>Interview (%)</th>
<th>Infant urine (%)</th>
<th>Meconium (%)</th>
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</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>100</td>
<td>61</td>
<td>96</td>
</tr>
<tr>
<td>Opiates</td>
<td>50*</td>
<td>38**</td>
<td>73*,**</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>54</td>
<td>34**</td>
<td>70**</td>
</tr>
<tr>
<td>Cannabis</td>
<td>21*</td>
<td>7**</td>
<td>50*,**</td>
</tr>
<tr>
<td>Cocaine</td>
<td>9</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>4</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>FAEESs</td>
<td>5*</td>
<td>–</td>
<td>47*</td>
</tr>
</tbody>
</table>

*p<0.05 meconium vs interview.

**p<0.05 meconium vs urine. Statistics were done using $\chi^2$ tests.

FAEEs, fatty acid ethyl esters.
Absolute risk of NAS

- prescription opiates only
  - 5.9 per 1000 live births (95% CI 5.6 to 6.2)
    - (no additional risk factors 4.2 per 1000 (3.3 – 5.4))
- + smoking - 6.6 per 1000 (4.3 to 9.6)
- + alcohol - 30.8 per 1000 (26.1 to 36.0)
- + other psychotropic medication - 13.1 (10.6 to 16.1)
- + opioid/other drug misuse - 220.2 (200.8 to 241.0)

Opioids and the fetus

- bad for growth
- multiple confounders
  - low maternal BMI / poor nutrition
  - smoking +/- alcohol
  - poverty
  - drug withdrawal
- probably not teratogenic
- endogenous opioids important in brain development

Liu AJW, Sithamparanathan S, Jones MP, Cook C-M, Nanan R. Arch Dis Child 2010
Morphine and the preterm infant

- no evidence of benefit from routine use (Cochrane)

100 ELBW babies

- high (n = 60) or low/no opioid (n = 40)
- high dose
  - ventilated for longer (53.5 v 45.6 days; p = 0.046)
  - more NEC (5% v 21.7%; p = 0.022)

multivariate analysis

- cumulative opioid dose associated with lower BSITD-III at 20 months (p = 0.012)
In utero growth: opioid-dependent pregnancies

- corrected reduction in birth weight 259 g
  - median z-score -0.61 (95% CI -0.52, -0.71)

- OFC reduced by 1.01 cm
  - median z-score -0.77 (95% CI -0.66, -0.89)

Hulse GK, Milne E, English DR, Hollman CD. Addiction 1997
Methadone-exposed (n=366) v Scottish pop (n=103,366)

Adjusted* difference in z-scores between the methadone exposed infants and the comparison group (derived from regression analysis)

<table>
<thead>
<tr>
<th></th>
<th>BWT z-score</th>
<th>OFC z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>- UCI</td>
<td>0.71</td>
<td>0.89</td>
</tr>
<tr>
<td>- LCI</td>
<td>0.52</td>
<td>0.66</td>
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<tr>
<td>Est.</td>
<td>0.61</td>
<td>0.77</td>
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</table>
Features of NAS

- mediated by noradrenaline release from locus coeruleus ("wakefulness nucleus")
- timing reflects the pattern of drug misuse
- multiple signs and symptoms
  - central nervous system
  - gastrointestinal
  - respiratory
  - poor feeding
- preterm babies also affected
Predicting NAS

- maintenance treatment
  - dose of methadone

- buprenorphine versus methadone
## Methadone vs buprenorphine

<table>
<thead>
<tr>
<th></th>
<th>Methadone (n = 89)</th>
<th>Buprenorphine (n = 86)</th>
<th>Odds Ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed study</td>
<td>73 (82%)</td>
<td>58 (67%)</td>
<td>0.02</td>
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<tr>
<td>Maternal age</td>
<td>27.7 ± 0.7</td>
<td>25.3 ± 0.7</td>
<td>0.014</td>
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<tr>
<td>Gestational age</td>
<td>37.9 ± 0.3</td>
<td>39.1 ± 0.3</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>14 (19%)</td>
<td>4 (7%)</td>
<td>0.3 (0.1-2.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>OFC</td>
<td>33.0 ± 0.3</td>
<td>33.8 ± 0.3</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>2878.5 ± 66.3</td>
<td>3093 ± 72.6</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>47.8 ± 0.5</td>
<td>49.8 ± 0.5</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Treated for NAS</td>
<td>41 (57%)</td>
<td>27 (47%)</td>
<td>0.7 (0.2-1.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>NAS peak score</td>
<td>12.8 ± 0.6</td>
<td>11.0 ± 0.6</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Total morphine (mg)</td>
<td>10.4 ± 2.6</td>
<td>1.1 ± 0.7</td>
<td>&lt;0.0091</td>
<td></td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>17.5 ± 1.5</td>
<td>10.0 ± 1.2</td>
<td>&lt;0.0091</td>
<td></td>
</tr>
</tbody>
</table>
Predicting NAS

- maintenance treatment
  
  *but less illicit drug use with buprenorphine*

  - less morphine treatment
  - shorter hospital stay

- extent and pattern of additional drug use

- abnormal maternal cardiac vagal tone

- genotype


Dryden C, Young D, Hepburn M, Mactier H. BJOG 2009
Wachman EM, Hayes MJ, Brown MS et al. JAMA 2013
### ECG/cardiac vagal tone

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean RR-ms (SD)</th>
<th>Mean HR-bpm (SD)</th>
<th>CVT (SD)</th>
<th>p-value</th>
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<tbody>
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<td><strong>Quiet Sleep</strong></td>
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<tr>
<td>Methadone-exposed</td>
<td>9</td>
<td>535.0 (35.2)</td>
<td>113.9 (9.6)</td>
<td>5.1 (1.6)</td>
<td>0.024</td>
</tr>
<tr>
<td>Controls</td>
<td>11</td>
<td>524.2 (32.2)</td>
<td>116.6 (7.2)</td>
<td>3.8 (0.9)</td>
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<tr>
<td><strong>Active Sleep</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone-exposed</td>
<td>7</td>
<td>541.0 (46.9)</td>
<td>111.5 (27.0)</td>
<td>5.5 (2.0)</td>
<td>0.0024</td>
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<tr>
<td>Controls</td>
<td>10</td>
<td>510.4 (25.1)</td>
<td>118.6 (5.6)</td>
<td>2.3 (0.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Indeterminate Sleep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone-exposed</td>
<td>11</td>
<td>540.8 (39.9)</td>
<td>112.3 (8.1)</td>
<td>5.5 (2.7)</td>
<td>0.0046</td>
</tr>
<tr>
<td>Controls</td>
<td>14</td>
<td>509.2 (32.5)</td>
<td>119.3 (10.6)</td>
<td>2.7 (0.3)</td>
<td></td>
</tr>
</tbody>
</table>

Standard deviations shown in brackets

Boulton R, Hamilton H, Bradnam MS, O'Regan M, Mactier H (unpublished)
All in the genes?

- ‘normal variant’ homozygous CYP2B6 genotype (fast metabolisers) more likely to require treatment for NAS
- no differences in CYP2D6, ABCB1, COMT or OPRM1

NO ACCURATE PREDICTOR OF NAS
Managing NAS

- keep mum and baby together
- encourage breast feeding
  - OR 0.55 (95% CI 0.34, 0.88; p=0.013)
  - beware codeine-using mothers
- caution around early discharge
  - 5 days’ stay
- scoring
  - advantages / limitations
  - no clearly defined threshold for treatment
  - consistency important

Smirk CL Bowman E, Doyle LW, Kamlin CO. J Paediatr Child Health 2014
Treating NAS

- Swaddling, rocking, pacifier, etc.
- Medication
  - Morphine, methadone
  - ....or buprenorphine?
    - Length of treatment 23 vs 32 days (p=0.01)
    - Length of stay 32 vs 42 days (p=0.05)
  - Or clonidine?
    - Shorter treatment compared to morphine (28 vs 39 days (p=0.02))
    - Better neurobehavioural performance at 2 - 4 weeks of age
      - But no differences at one year
- Adjuvant phenobarbital

Osborn DA, Jeffery HE, Cole MJ. Cochrane Database Syst Rev. 2010
Agthe AG, Kim GR, Mathais KB et al. Pediatr 2009
Kraft WK, Gibson E, Dysart K et al. Pediatr 2008
Hospital or home?

- majority of UK neonatal units do not discharge babies on treatment
- methadone home medication associated with
  - improved breast feeding rates
  - 50% reduction in hospital stay
- oral morphine
  - shorter hospital stay
  - longer duration of treatment
- beware two preparations of phenobarbital
  - 50mg/5ml and 15mg/5ml

Discharge

- social work and health visitor involvement
- demand feed
  - not second stage formula
- hepatitis B vaccine
- benign sleep myoclonus common
- SUDI
  - opioid toxicity
  - overlaying
  - maternal smoking
  - OR 1.45 (95% CI 0.47, 4.46)

Toxicology

- what?
  - urine
  - meconium
    - most sensitive
    - expensive

- when?
  - seizures – undiagnosed
  - unexplained hypertension

- disclosure
Not just jittery......

- unseen features of *in utero* drug exposure
- methadone-exposed infants versus controls
  - more immature waveforms (p<0.001)
  - VEPs smaller (27 v 39 µV (p<0.001))
- NO relationship to
  - prescribed dose of methadone at delivery
  - poly-drug use
  - severity of NAS

Other electrophysiology

- **ECG**
  - reduced fetal HR variability and ↓ fetal movements
  - prolonged QT interval (day 1 - 2)
  - increased cardiac vagal tone
- **EEG**
  - abnormal sleep studies (adults & animals)
  - neonates
    - disordered sleep pattern
    - excess sharp waves

Boulton R, Hamilton H, Bradnam MS, O’Regan M, Mactier H (unpublished)
Gene methylation – *OPRM1*

**mums**

- **OPRM1 Promoter**
- **OPRM1 +12**

**babies**

- **OPRM1 Promoter**
- **OPRM1 +12**

- affluent
- deprived
- methadone-exposed

*P < 0.005*
Gene methylation – *ABCB1*

**mums**

- $P = .934$
- $P = <.0005$
- $P = .0005$
- $P = .953$

**babies**

- $P = .953$
- $P = <.0005$
- $P = .934$
- $P = <.0005$
Gene methylation – *CYP2D6*

- ↑methylation of at least 5 opioid-related genes (baby)
- no relationship to NAS
The longer term

- with or without NAS
Growth in childhood

- OFC tends to catch up by 6 months
- some evidence of reduced height at 3 years
- social confounders +++

Visuo-cortical function at 6 months

- 81 methadone-exposed; 26 comparison
  - 79% and 52% of original cohort
- pattern onset VEPs (three check sizes)
Presence of VEPs

VEPs in methadone-exposed babies smaller (p<0.0002) and slower (p<0.003)
(Lack of) effect of *in utero* drug exposure
Is buprenorphine better?

- controls (n=33), methadone (n=30) and buprenorphine (n=20) maintained pregnancies
- VEP latency at 4 months of age (48' checks) prolonged in methadone-exposed infants

**but**

- methadone-exposed infants less mature
  - 14.95 ± 2.02 versus 16.76 ± 4.20 weeks
- non-randomised

- no differences at 3 years!

Whitham JN, Spurrier NJ, Sawyer MG et al. Neurotoxicology and Teratology 2010
Whatham JN, Spurrier NJ, Baghurst PA et al. Neurotoxicology and Teratology 2015
Infant vision development

- reduced visual acuity
- nystagmus
- strabismus
  - 10x more common (at least)
- delayed visual maturation
- cerebral visual impairment
- lack of binocularity

Mulvihill AO, Cackett PD, George ND, Fleck BW. B J Ophthalmol 2007
Prospective cohort study – 6 months

- 82 methadone-exposed infants
- 40% failed clinical visual assessment
  - RR 5.0 (95% CI 1.3, 20; p=0.02)
- further 11% borderline
- 25% strabismus; 22% reduced visual acuity
- 11% nystagmus
  - manifest in 5, latent in 4
  - 300 x greater than general population incidence

*2 children exposed only to methadone in utero failed visual assessment
And at 5 years.....

- 301 children born 2000 – 2004
  - 96 (31.9%) previously referred to ophthalmology
  - 7887 controls (13.1% referred)
- 5 year follow up (8 lost, 3 discharged)
  - Strabismus
    - Prevalence (42/301) 14.0 versus 2.8%
    - OR 5.7 (95% CI 4.01, 8.12)
  - Nystagmus
    - Prevalence (10/301) 3.3 versus 0.004%
    - OR 90.3 (95% CI 24.7, 330)

Neuroimaging - MRI

- differences in DTI at 3-4 weeks of age and at 10 years
  - consistent with altered maturation of connective tracts
  - some correlation with cognitive function
  - confounded by gestation
- thalami increased in size in mid-gestation in opioid-exposed human fetuses
- smaller brains at term
  - whole brain and basal ganglia volumes

Walhovd KB, Westlye LT, Moe V, Slinning K et al., AJNR 2010
General development

- maternal opiate use linked with
  - motor developmental delay
  - low IQ
  - behavioural problems
  - cerebral palsy
  - ADHD
- *but* studies confounded by
  - small numbers
  - poor rates of follow up
  - social factors

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Konijnenberg C, Melinder A. Child Neuropsychol 2011
Van Baar A and de Graaf BMT. Dev Med Child Neurol 1994
Hunt RW Tzioumi D, Collins E, Jeffery HE. Early Human Dev 2008
## VIDI cohort

<table>
<thead>
<tr>
<th>Development</th>
<th>Cases (n=81)</th>
<th>Controls (n=26)</th>
<th>p-value</th>
<th>Adjusted p-value</th>
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<tbody>
<tr>
<td>Locomotor</td>
<td>102 (93-107)</td>
<td>111 (101-111)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
<tr>
<td>Personal-social</td>
<td>94 (88-96)</td>
<td>99 (94-103)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Language-hearing</td>
<td>105 (105-109)</td>
<td>109 (105-109)</td>
<td>&lt;0.001</td>
<td>0.007</td>
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<tr>
<td>Eye-hand</td>
<td>94 (86-99)</td>
<td>104 (99-104)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Performance</td>
<td>96 (86-100)</td>
<td>101 (101-111)</td>
<td>&lt;0.001</td>
<td>0.002</td>
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<tr>
<td>GQ</td>
<td>97 (93-100)</td>
<td>105 (101-108)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Medians (inter-quartile ranges). Corrected for maternal smoking, antidepressant use and excess alcohol consumption in pregnancy.

McGlone L, Mactier H. Early Human Dev 2105
Erratum: Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis

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COGNITION: Opioid exposed compared to non-opioid exposed preschool children

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Std diff in means</th>
<th>Standard error</th>
<th>Variance</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt et al (2016)</td>
<td>5 years old</td>
<td>Mc, CARTv</td>
<td>0.515</td>
<td>0.117</td>
<td>0.119</td>
<td>0.840</td>
<td>3.613</td>
<td>0.000</td>
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<tr>
<td>Omary et al (2014, 2000)</td>
<td>5 years old</td>
<td>Mc, CARTv</td>
<td>0.078</td>
<td>0.120</td>
<td>0.067</td>
<td>0.181</td>
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<tr>
<td>Ma et al (2016)</td>
<td>4.5 years old</td>
<td>Mc, CARTv</td>
<td>0.111</td>
<td>0.200</td>
<td>0.089</td>
<td>0.235</td>
<td>0.075</td>
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<tr>
<td>Watford et al (2011)</td>
<td>4.5 years old</td>
<td>Mc, CARTv</td>
<td>0.000</td>
<td>0.141</td>
<td>0.072</td>
<td>0.232</td>
<td>0.812</td>
<td>0.009</td>
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</table>

Figure 4 COGNITION: Opioid exposed compared to non-opioid exposed preschool children.
**PSYCHOMOTOR: Opioid exposed infants compared to non-opioid exposed infants**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Outcome</th>
<th>Statistics for each study</th>
<th>95% CI in means and 95% CI</th>
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<tbody>
<tr>
<td>Hatt et al (2008)</td>
<td>1.5 years old</td>
<td>BSD (Pyschomotor)</td>
<td>0.170</td>
<td>0.171</td>
</tr>
<tr>
<td>Szewczak et al (2016)</td>
<td>1 year old</td>
<td>G2S (Locomotor)</td>
<td>0.687</td>
<td>0.213</td>
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<tr>
<td>Mor et al (2002)</td>
<td>1 year old</td>
<td>BSD (Pyschomotor)</td>
<td>0.591</td>
<td>0.191</td>
</tr>
<tr>
<td>Harm et al (2001)</td>
<td>1 year old</td>
<td>BSD (Pyschomotor)</td>
<td>0.274</td>
<td>0.230</td>
</tr>
<tr>
<td>Hans et al (2001)</td>
<td>2 years old</td>
<td>BSD (Pyschomotor)</td>
<td>0.549</td>
<td>0.253</td>
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</table>

Favours opioid exposed infants  
Favours non-opioid exposed infants

**Figure 2 PSYCHOMOTOR: Opioid exposed infants compared to non-opioid exposed infants.**

**PSYCHOMOTOR: Opioid exposed compared to non-opioid exposed preschool children**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Outcome</th>
<th>Statistics for each study</th>
<th>95% CI in means and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hatt et al (2008)</td>
<td>3 years old</td>
<td>Moorg Motor Scale</td>
<td>0.490</td>
<td>0.196</td>
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<tr>
<td>Orthey et al (2000)</td>
<td>5 years old</td>
<td>Moorg Motor Scale</td>
<td>0.970</td>
<td>0.511</td>
</tr>
<tr>
<td>Mor et al (2000)</td>
<td>6.5 years old</td>
<td>Moorg Motor Scale</td>
<td>0.720</td>
<td>0.190</td>
</tr>
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</tbody>
</table>

Favours opioid exposed children  
Favours non-opioid exposed children

**Figure 5 PSYCHOMOTOR: Opioid exposed compared to non-opioid exposed preschool children.**
and for pre-school children....
Executive function

- 66 children, 48 – 57 months
  - 35 prenatally exposed to opioid maintenance
- Neuropsychological tests + BRIEF-P
- Opioid-exposed children
  - Less good at tasks of short term memory and inhibition
  - Poorer executive function
- NB all scores WNL!

2008 - “methadone treatment throughout pregnancy does not have adverse effects on postnatal development”

2012 - “methadone (substitution treatment) is safe and effective in terms of consistently better obstetric and perinatal outcomes……The only complication for the baby is a risk of neonatal abstinence syndrome, readily managed with withdrawal management and supportive care”
Summary

- *in utero* opioid exposure is associated with:
  - adverse effects on visuo-cortical function which persist throughout infancy and into early childhood
  - impairment of cognitive, psychomotor and behavioural development in infancy and the pre-school years

- *in utero* opioid-exposed neonates merit follow up

- methadone may not be the best treatment for pregnant opioid-dependent women
Acknowledgements

- Ruth Hamilton, Michael Bradnam and Richard Boulton, Royal Hospital for Sick Children and University of Glasgow
- Daphne McCulloch, Glasgow Caledonian University
- Laura McGlone & Jane MacKinnon
- Gail Cooper and the Forensic Medicine and Science team at Glasgow University
- Yorkhill Children’s Charity
- Glasgow Royal Infirmary Appeals Trust
- TENOVUS Scotland
- Robertson Trust
Thank you!

Any questions?