Micro-dosing versus standard transfer for methadone-buprenorphine transfers - results from an open-label, non-randomised clinical trial

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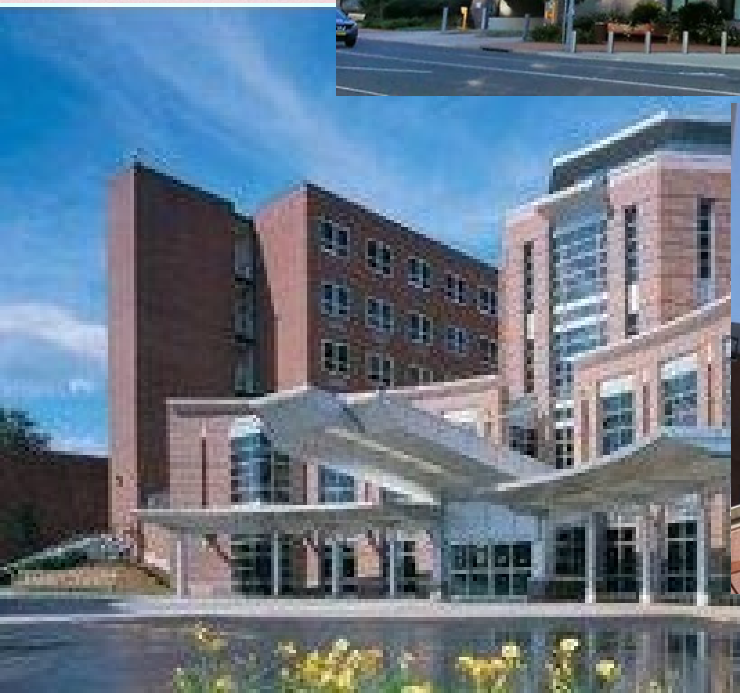
Thanks

- My patient wife
- Prof Paul Haber
- Susan Anderson
- Dr James Blogg
- Dr Nazila Jamshidi
- Dr Llewelyn Mills
- Prof Nicholas Lintzeris
- Dr Ricky Harjanto
- Charlotte Ismay
- Dr Alison Blazey
- Dr Rob Page


St Vincent's Hospital


CANTERBURY
HOSPITAL
EMERGENCY


RNS Community Health Centre

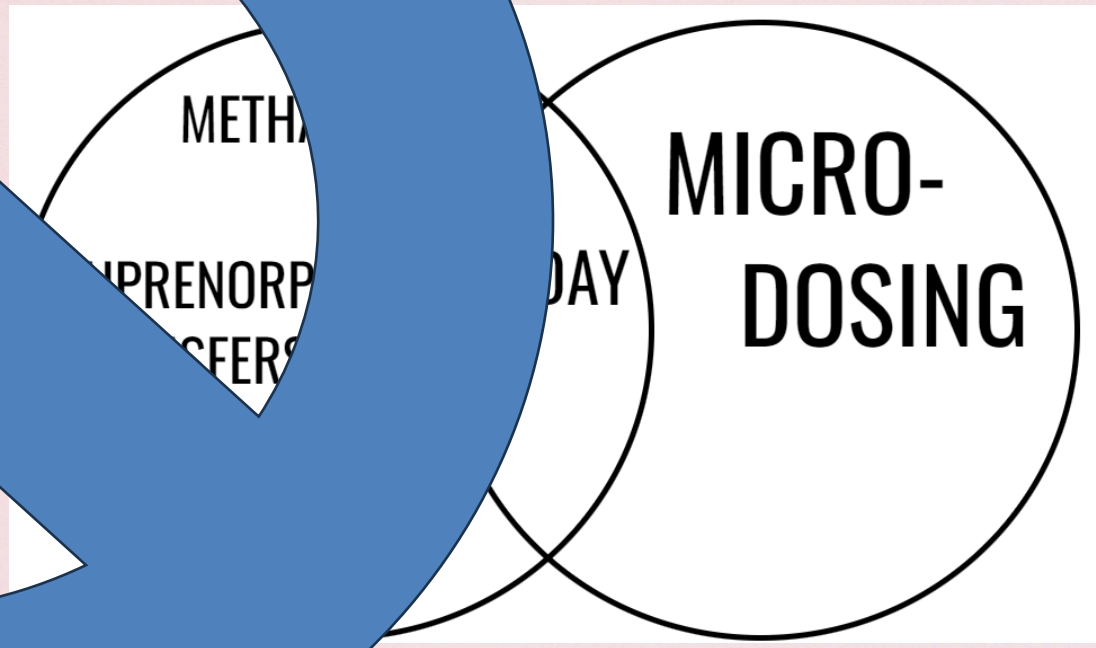



Liverpool
Hospital
EMERGENCY
Entrance
C, D, E, F, G


JOHN HUNTER HOSPITAL

Today

- Backgroun ne-buprenor
- Backgro micro
- Backgro micro-dos AND me e-buprenorp transfers
- Results fr udy
- Factors in go sfers



Dear Dr Chris Tremonti,

Re: JAM-D-23-00422R2 (Methadone-Buprenorphine Transfers using Low-dosing of Buprenorphine: An Open-label, Non-randomised Clinical Trial)

Your article has been accepted for publication in Journal of Addiction Medicine. I will manage its production through all of its stages from now until publication. Please contact me should any queries arise.

Trial registered on ANZCTR

Micro-dosing with buprenorphine to transfer from methadone to buprenorphine

- Prospective
- Multi-centre
- Non-randomised – choice of transfer method
- Patients on methadone for at least five days wishing to switch to BPN
- Primary outcome: completion
  - On buprenorphine 7 days post micro-dose transfer OR
  - On buprenorphine 7 days post initiation in standard transfer arm

- Secondary outcomes
  - Opioid withdrawal
    - COWS
    - SOWS
  - Rates of precipitated withdrawal
  - Ambulatory transfers
  - PRN medication use
  - Change in substance use
  - Predictive factors for successful transfer***

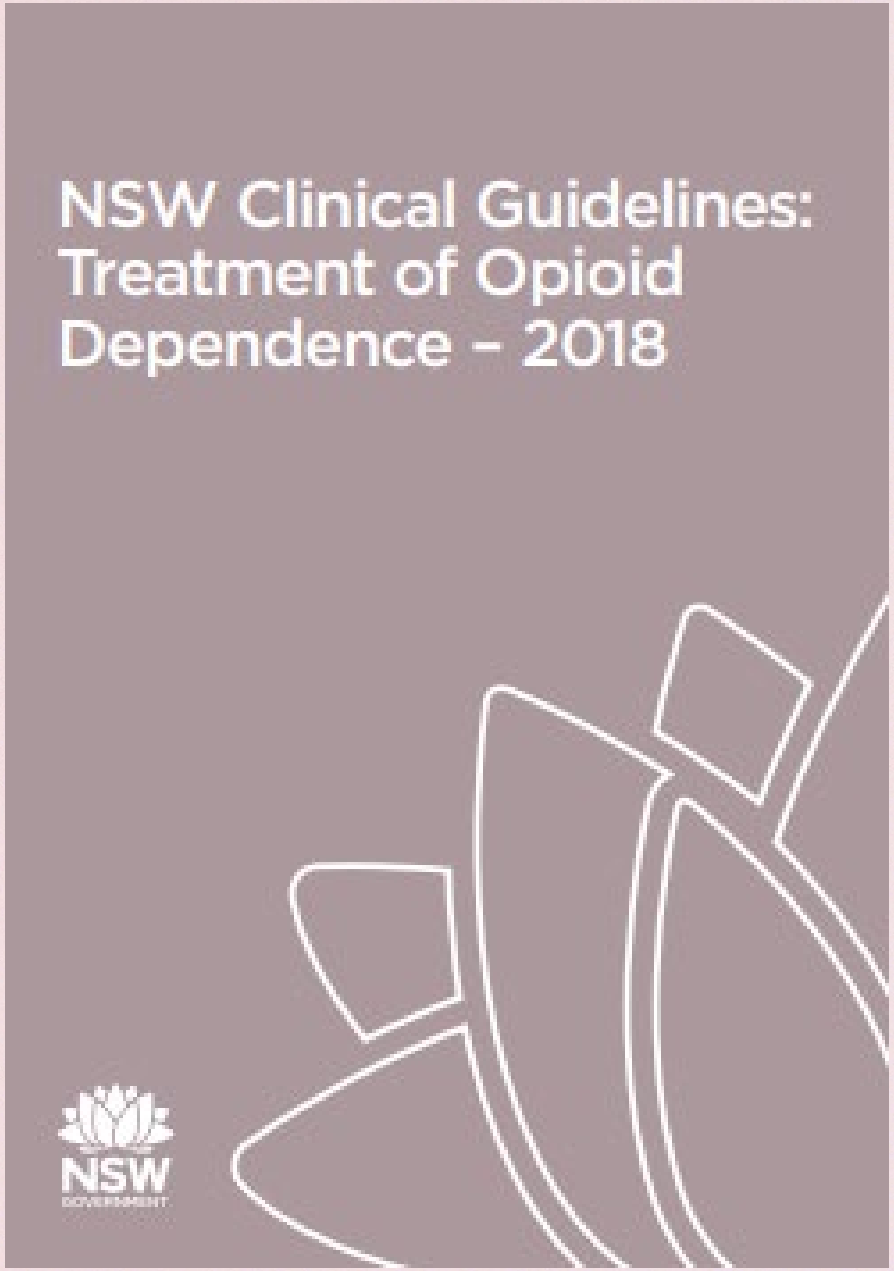

Patient interested in switching from methadone to buprenorphine
Screening - consent if appropriate
Does the patient have a preference for method of transfer
Yes - Micro-dosing
No - standard of care
Yes - standard of care
Does the patient want inpatient or outpatient transfer?
Is the patient on >60mg methadone?
Outpatient
Inpatient
Yes - inpatient transfer
No - outpatient transfer
Day 1 assessment
Day 1 assessment
Microdosing protocol (see next box)
Standard of care
Discharged from hospital to continue buprenorphine
1 week follow up
1 month follow up

Micro-dose protocol

Micro-dosing Protocol		
Day	Methadone Dose	Buprenorphine Dose
Day 1	Xmg	0.2mg BD
Day 2	Xmg	0.4mg BD
Day 3	Xmg	2mg
Day 4	Xmg	4mg
Day 5	Xmg	8mg
Day 6	½ Xmg	16mg
Day 7	¼ Xmg	16-32mg

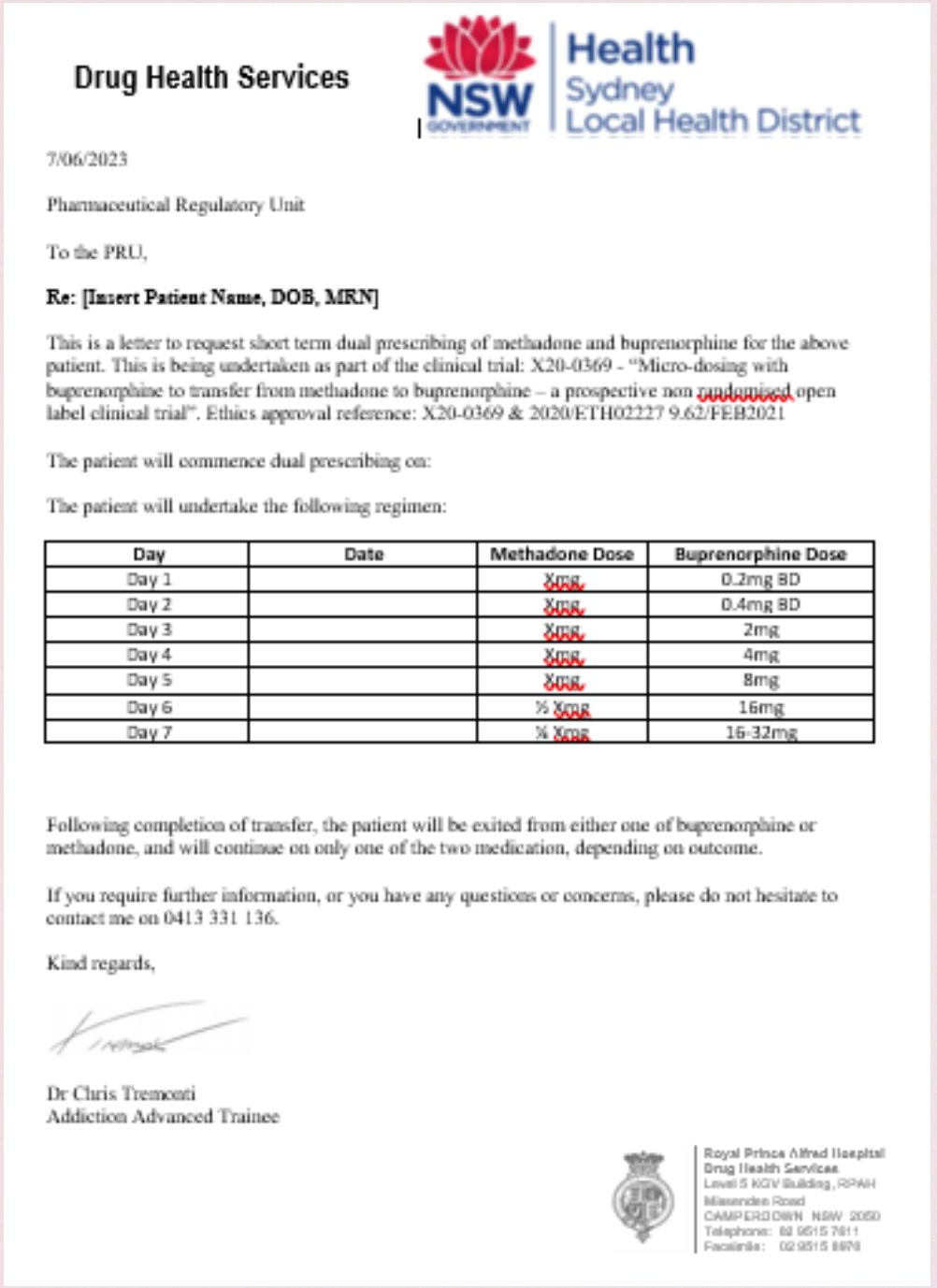
Standard of Care

- Stop methadone
- Wait for COWS score 13 or more
- Commence 2mg BPN
- Up to 32mg day one



Protocol

- Subutex (not suboxone)
- Patients given pack of:
  - Clonidine 50mcg x 4
  - Ondansetron 8mg wafers x 2



Drug Health Services

NSW GOVERNMENT Health Sydney Local Health District

7/06/2023

Pharmaceutical Regulatory Unit

To the PRU,

Re: [Insert Patient Name, DOB, MRN]

This is a letter to request short term dual prescribing of methadone and buprenorphine for the above patient. This is being undertaken as part of the clinical trial: X20-0369 - "Micro-dosing with buprenorphine to transfer from methadone to buprenorphine – a prospective non randomised open label clinical trial". Ethics approval reference: X20-0369 & 2020/ETH02227 9.62/FEB2021

The patient will commence dual prescribing on:

The patient will undertake the following regimen:

Day	Date	Methadone Dose	Buprenorphine Dose
Day 1		Xmg OOOL	0.2mg BD
Day 2		Xmg OOOL	0.4mg BD
Day 3		Xmg OOOL	2mg
Day 4		Xmg OOOL	4mg
Day 5		Xmg OOOL	8mg
Day 6		½ Xmg OOOL	16mg
Day 7		½ Xmg OOOL	16-32mg

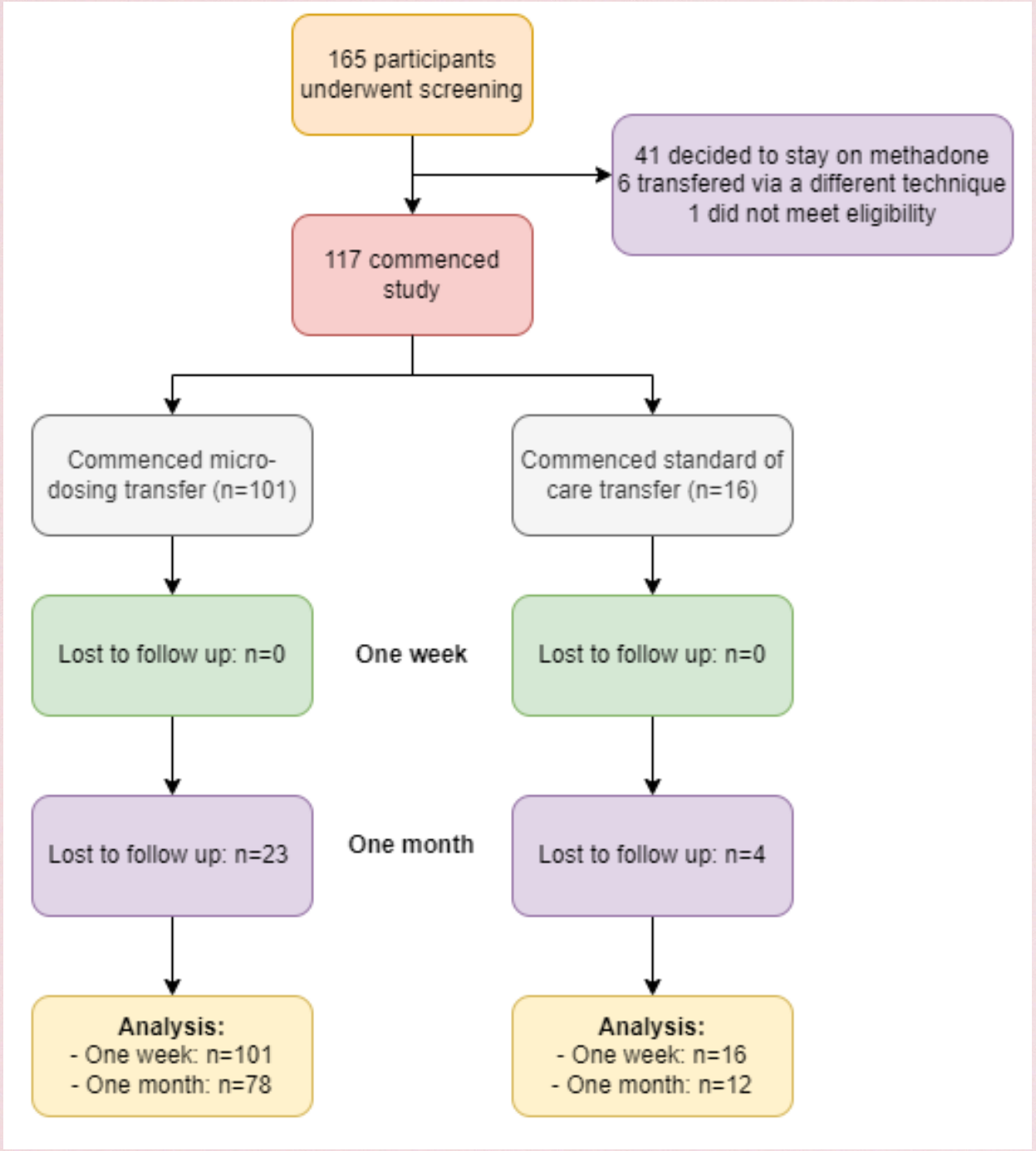
Following completion of transfer, the patient will be exited from either one of buprenorphine or methadone, and will continue on only one of the two medication, depending on outcome.

If you require further information, or you have any questions or concerns, please do not hesitate to contact me on 0413 331 136.

Kind regards,

Dr Chris Tremonti
Addiction Advanced Trainee

Royal Prince Alfred Hospital
Drug Health Services
Level 5 KGV Building, RPAH
Missenden Road
CAMPERDOWN NSW 2050
Telephone: 02 9515 7611
Facsimile: 02 9515 8879


165 participants underwent screening
41 decided to stay on methadone
6 transfered via a different technique
1 did not meet eligibility
117 commenced study
Commenced micro-dosing transfer (n=101)
Commenced standard of care transfer (n=16)
Lost to follow up: n=0
One week
Lost to follow up: n=0
Lost to follow up: n=23
One month
Lost to follow up: n=4
Analysis:
- One week: n=101
- One month: n=78
Analysis:
- One week: n=16
- One month: n=12

Demographics

	Micro-dosing	Standard Care
Age, mean	43.7	44.5
Baseline methadone dose, mean, mg	**82.3**	**46.3**
Male, No. (%)	68 (67)	11 (69)
Indigenous, No. (%)	20 (20)	3 (19)
BMI, mean, kg/m^2	28.8	26.6
Time on methadone, median months	72	50
Self-report drug use, median No.	2	2
Methadone trough, mean (SD), ng/ml	**345.4 (259.5)**	**170.3 (104.8)**

Demographics

	Micro-dosing	Standard Care
Craving VAS, median (100)	2	0
K10, mean	25.2	21.4
Expectations of withdrawal for the study, mean VAS	47	46.9
Experience of withdrawal symptoms, mean VAS	73.8	67.7
Withdrawal expectations if ceased all opioids, mean VAS	74.9	81.9
Renal dysfunction, n (%)	15 (15)	2 (13)
Liver dysfunction, n (%)	1 (1)	0 (0)

Raw Results

	Micro-dosing (n = 101)	Standard care (n = 16)
Primary – dosed BPN one week post transfer, No., (%)	**81 (80)**	**13 (81)**
COWS >12, N (%)	25 (25)	1 (6)
SOWS-Gossop Change >4, N (%)	**53 (52)**	**10 (63)**
Dosed buprenorphine one month post transfer, N (%)	78 (77)	12 (75)
% on depot buprenorphine, N (%)	73 (72)	10 (63)
Ambulatory transfers, N (%)	58 (57)	13 (81)
- **Ambulatory transfer success, N (%)**	**49 (85)**	**12 (92)**
Precipitated withdrawal, N (%)	4 (4)	1 (6)
Patient satisfaction, median VAS	90	84

Regression analysis of outcomes

- Comparison between arms confounding for:
  - Starting methadone dose
  - Time on methadone
  - Alcohol and benzodiazepine use in the previous 28 days
  - Serum methadone trough level

	Micro-dosing n = 101	Standard-Care n = 16	Adjusted Odds ratio (95% CI)	Unadjusted Odds Ratio (95% CI)
Dosed BPN one week No., (%)	81 (80%)	13 (81%)	**2.22 (0.45, 10.91)**	0.935 (0.24, 3.6)
Moderate withdrawal as per COWS (>12), N (%)	25 (25%)	1 (6%)	**3.01 (0.32, 28.5)**	3.94 (0.49, 31.5)
SOWS-Gossop Change >4, N (%)	53 (52%)	10 (63%)	**1.29 (0.36, 4.6)**	0.81 (0.27, 2.4)
Dosed BPN one month, N (%)	78 (77%)	12 (75%)	**3.28 (0.73, 14.8)**	1.44 (0.42, 5)
Precipitated withdrawal, N (%)	4 (4%)	1 (6%)	**0.46 (0.03, 7.18)**	0.62 (0.07, 5.91)
Satisfaction, median (IQR), VAS	90 (75-100)	84 (63-94)	**6.08 (-7.23, 19.4)**	2.73 (-9.39, 14.8)
Change in craving, mean, VAS	8.86 (33.9)	4.93 (16.5)	**-2.71 (-22.4, 16.9)**	3.93 (-13.2, 21)

Rescue Medication use, N who used (%), median dose across the transfer period	Micro-dosing n = 101	Standard-Care n = 16	Adjusted Odds ratio (95% CI)	Unadjusted Odds Ratio (95% CI)
- Clonidine	**71 (70), 500mcg**	**2 (13), 250mcg**	**527 (268, 785)**	**423 (146, 700)**
- Diazepam	51 (50), 45mg	4 (25), 10mg	27.2 (-9.85, 64.2)	32.4 (-3.74, 68.5)
- Ondansetron	**47 (47), 24mg**	**3 (19), 16mg**	**1.97 (0.06, 23.4)**	**1.99 (0.21, 21.6)**
- Paracetamol	37 (37), 4000mg	1 (6), 1000mg	0.85 (-0.96, 2.42)	2.05 (0.08, 3.31)
- Ibuprofen	16 (16), 1800mg	1 (6), 400mg	-0.22 (-436, 348)	1.31 (-126, 635)
- Metoclopramide	16 (16), 20mg	1 (6), 10mg	0.43 (-7.25, 11.4)	1.15 (-3.61,13.9)

Simplified…

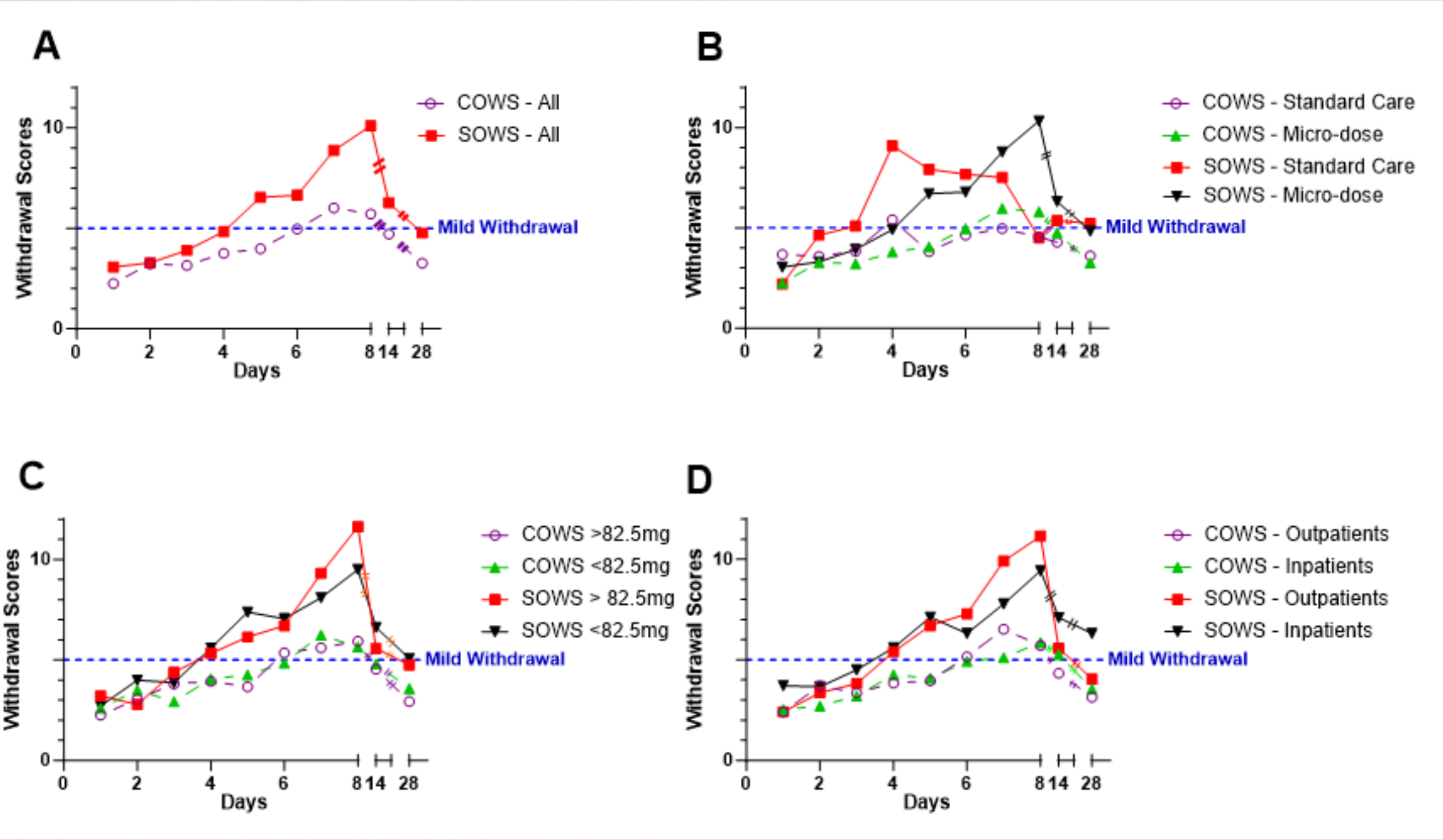
- No difference in outcome micro-dose v standard transfer
- Increase methadone dose 10mg reduced odds of one-week completion by 20% - not seen at four weeks
- Increased clonidine use
- No participant chose randomisation
- Over half experienced subjective withdrawal
- Highest daily dose for successful micro-dose transfer was 140mg
- 24 (80%) of the participants prescribed 100mg of methadone or more completed transfer

Incomplete Transfers

	Low-dosing - n = 20(20%)	Standard-Care - n = 3 (19%)
Development of withdrawal discomfort such that participant requested return to methadone	7	0
Discharged against medical advice, no stated withdrawal symptoms	5	1
Precipitated withdrawal	3	1
Discharged from hospital due to aggression	1	1
Benzodiazepine withdrawal seizure	1	0
Discontinued all OTP	1	0
Persistent missed dosing	1	0
Anxiety from external stressor	1	0

Changes in substance use

Substance	Micro-dosing	Standard Practice	p value
Alcohol			
- Increase	7	0	0.369
- No change	64	9	
- Decrease	4	1	
THC			
- Increase	8	0	0.573
- No change	58	11	
- Decrease	8	0	
CMA			
- Increase	7	0	0.300
- No change	67	10	
- Decrease	0	0	
BZDs			
- Increase	9	0	0.028
- No change	59	9	
- Decrease	6	1	


A
Withdrawal Scores
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2
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14
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Days
COWS - All
SOWS - All
Mild Withdrawal
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Withdrawal Scores
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Days
COWS - Standard Care
COWS - Micro-dose
SOWS - Standard Care
SOWS - Micro-dose
Mild Withdrawal
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COWS >82.5mg
COWS <82.5mg
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Mild Withdrawal
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Withdrawal Scores
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8
14
28
Days
COWS - Outpatients
COWS - Inpatients
SOWS - Outpatients
SOWS - Inpatients
Mild Withdrawal

Predictors of success*****

- All demographical information
  - Age, gender, Indigenous status
  - Methadone dose
  - Withdrawal expectations
  - Cravings
  - K10
  - Method of transfer
  - Medications
  - Substance use
    - Alcohol
    - Methamphetamines
    - THC
    - Opioids
    - Injecting drug use…….

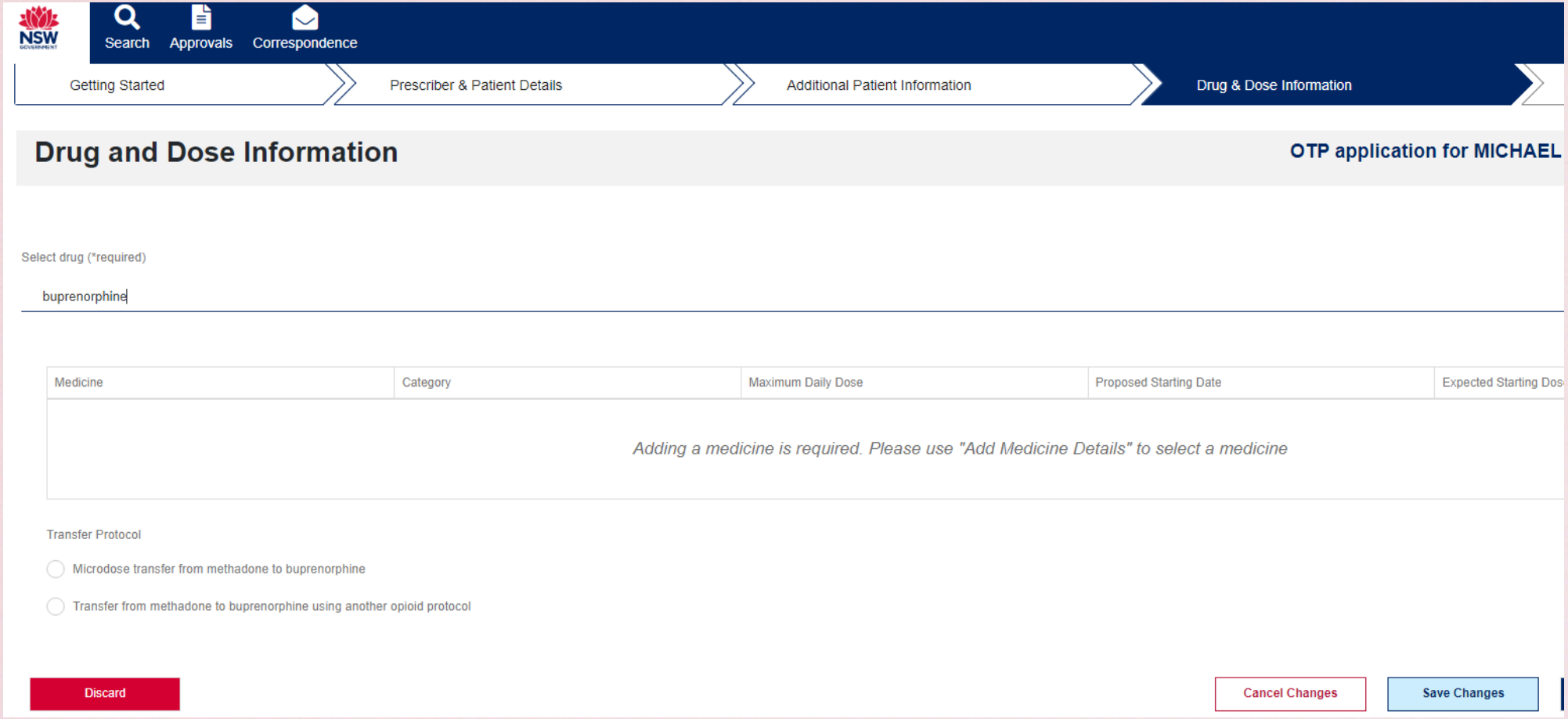

drum roll
please...

APSAD 2025

DECOLONISING
DISRUPTING
DECONSTRUCTING

My Experiences and Conclusions

- Micro-dosing is an option for patients on higher doses, and those wanting to undertake ambulatory methadone-buprenorphine transfers
- Remains unclear what the best method for methadone-buprenorphine transfer is - options
- Don’t pressure patients to transfer
- Clinician experience key
- Subjective withdrawal is the norm, not the exception, so prepare for it
- Minimal withdrawal first 3 days – start on Thursday/Friday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Search
Approvals
Correspondence
Getting Started
Prescriber & Patient Details
Additional Patient Information
Drug & Dose Information
Drug and Dose Information
OTP application for MICHAEL
Select drug (*required)
buprenorphine
Medicine
Category
Maximum Daily Dose
Proposed Starting Date
Expected Starting Dos
Adding a medicine is required. Please use "Add Medicine Details" to select a medicine
Transfer Protocol
Microdose transfer from methadone to buprenorphine
Transfer from methadone to buprenorphine using another opioid protocol
Discard
Cancel Changes
Save Changes