

Do pharmacological interventions reduce drugs-related deaths ?

How do we find out . . .

Powerful, well-designed RCTs
Record-linkage studies – caveats ?

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Epidemiology Matters!

Injecting Drug Users (IDUs) – UK Heroin
Male; ageing 1980s-epidemic-wave of IDUs

Drugs-Related Deaths (DRDs) – Opiates
IDUs; 80% M; co-present alcohol/benzos;
age-related increase in DRD-rate!

Opiate Substitution Therapy (OST) –
mainly methadone. Off-injecting reduces
BBV/DRD risks; off-heroin reduces **crime!**

Scotland

(population of 5 millions)

HIV/AIDS deaths

?

Scotland's rising tide of opiate-related DRDs: demography

Subgroup	female	MALE	<25 M	25-34M	35-44M	45+ yr M
4 years of 2006-09: 1,994 DRDs (1,571 opiates)						
All DRDs	394	1,600	261	575	513	251
Opiates	280	1,291	211	490	418	172
<i>Per year</i>	<i>70</i>	<i>323</i>	<i>53</i>	<i>123</i>	<i>104</i>	<i>43</i>
6 years of 2000-05: 2,018 DRDs (1,554 opiates)						
All DRDs	386	1,632	381	659	433	159
Opiates	240	1,314	304	556	354	100
<i>Per year</i>	<i>40</i>	<i>219</i>	<i>51</i>	<i>93</i>	<i>59</i>	<i>17</i>

Scotland's recent OD4-methadone index?

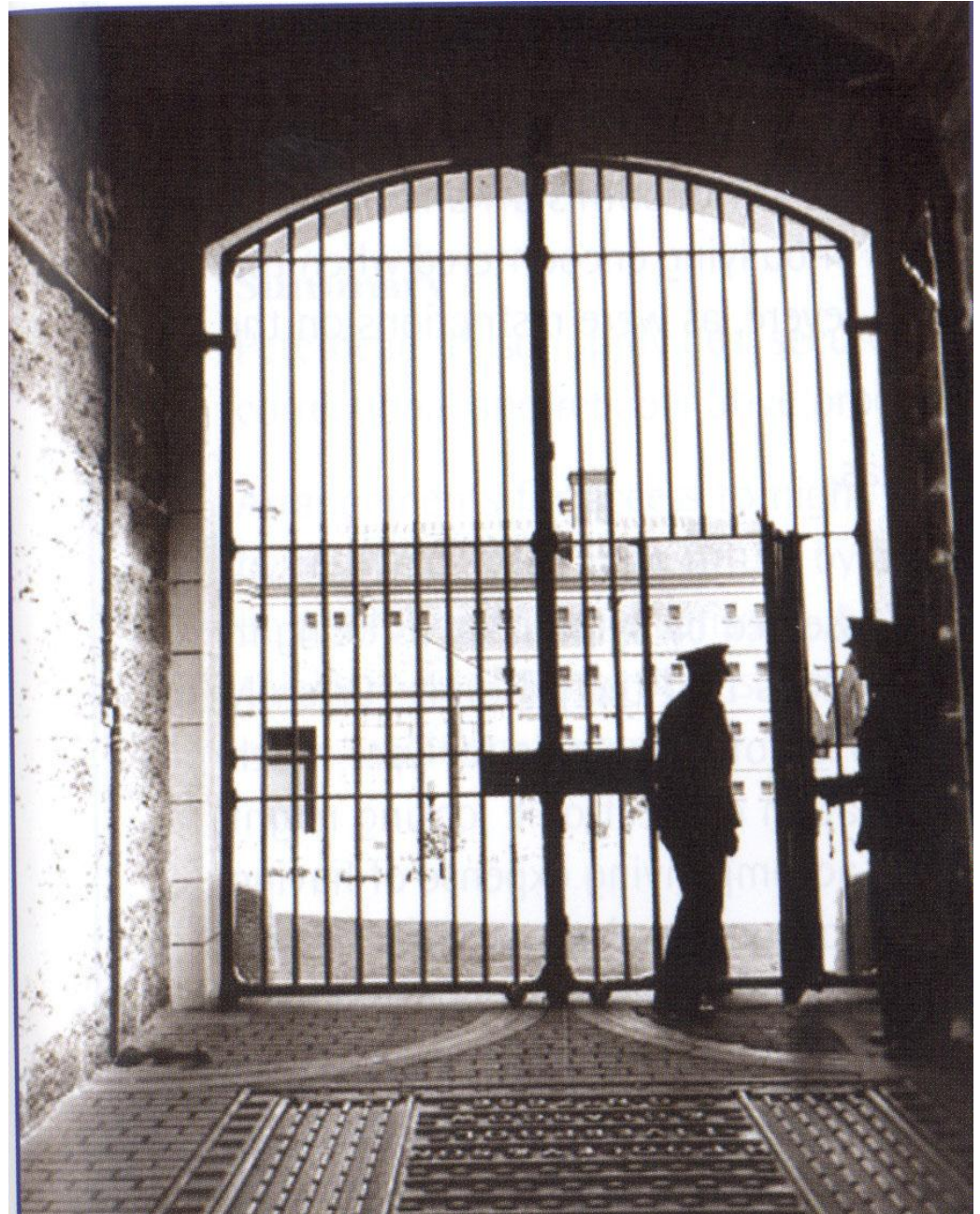
Methadone implicated deaths per 1m defined daily doses of methadone prescribed (Strang et al, BMJ)

OR **per 1,000 implied methadone-patient-years**

EPOCH	1993-96	1997-00	2001-04	2005-08	2009-11: 3 years
Methadone-related DRDs, MRDs	237	269	337	464	622
Methadone prescribed (mg* 1 million; M-DDD = 60 mg)	245.6	559.1	1136.3	1988.1	2010/11: 637.4
Implied methadone-patient-yrs, mpys	11215	25530	51889	90781	2010/11: 29.1K 83728 + mpys
MRDs per 1,000 mpys	21 (95% CI: 18- 24)	11 (95% CI: 9- 12)	6.5 (95% CI: 5.8-7.2)	5.1 (95% CI: 4.6-5.6)	7.4 (95% CI: 6.8-8.0)

HMP Edinburgh

WASH
surveillance
(1991-96)



1991 WASH



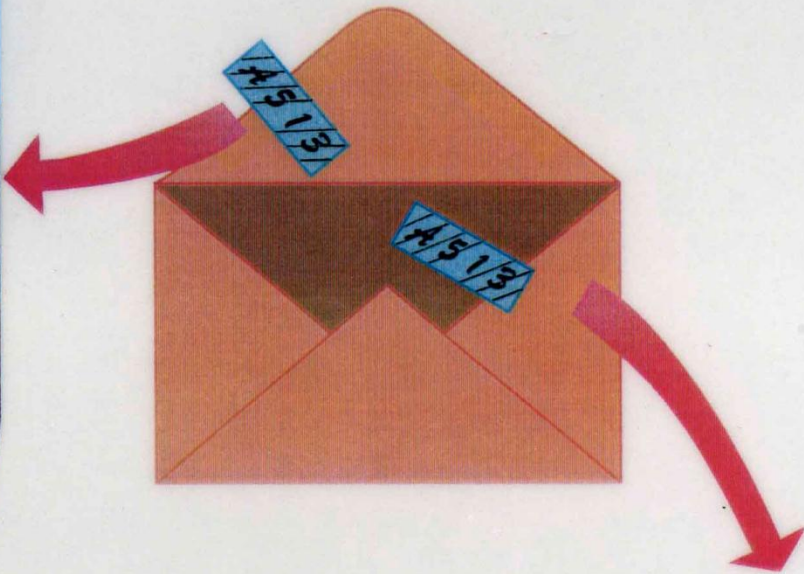
Willing *[ethical]*

Anonymous
[no deductive disclosure]

Saliva & linked self-Q
[high volunteer rate]

HIV surveillance

Linked to self-Q on risks
[frank answers]



Anonymous HIV surveillance in HM Prison Glenochil

Thank you for your help in this study which will enable us to plan better HIV care in prisons. We do not need to know your name nor any other form of identification when you complete this questionnaire. It goes to the Medical Research Council for analysis. No results will be reported which relate to fewer than 30 prisoners.

Please tick (✓) the box beside the answer that applies to you

1 How old are you? under 26 years
26-30 years
31-35 years
36-40 years
over 40

2 Where did you live before coming into Glenochil Prison?
 Glasgow: Springburn, Maryhill, Possilpark. Edinburgh
Ruchill
 Glasgow: Easthouse Dunoon
 Glasgow: Castlemilk Fife
 Glasgow: Garhale, Govan, Mitchell, Pollock elsewhere
 rest of Glasgow

3 How long is your present sentence? less than 1 year
between 1 and 3 years
more than 3 years

4 When did your present sentence begin? in 1994
in 1993
in 1991 or 1992
in 1990 or 1989 or 1988 or 1987
in 1985 or 1983 or 1984 or 1983
before 1983

5 Were you in Glenochil Prison at any time during January to June last year (1993)? yes
no

6 How many times have you been inside before this sentence? never
once
2 or 3 or 4 times
5 or more times

7 Have you been in a hospital or young offenders' institution? yes
no

8 Have you ever been charged with a drugs-related offence? yes
no

9 How much time have you done inside since January 1983? less than 6 months
between 7 and 12 months
between 1 and 3 years
more than 3 years

A/S/B

Please fix sealed label here.



10 In which year did you first inject drugs (excluding insulin)? NEVER INJECTED
1982 or earlier
1983-1985
1986-1988
1989-1991
1992 or later

11 In which year did you last inject? NEVER INJECTED
1982 or earlier
1983-1985
1986-1988
1989-1991
1992 or later

12 Have you ever injected while inside? yes
no

13 Did you start injecting while inside? yes
no

14 Did you inject in Glenochil Prison during January to June last year (1993)? yes
no

15 Have you ever taken the blood test for HIV? yes
no

16 Did you have an HIV blood test in Glenochil Prison during January to June last year (1993)? yes
no

17 Have you had an acute attack of hepatitis or yellow jaundice? yes
no

18 In the last year before this sentence, how many women did you have sex with? none
1
2-5
6-10
11 or more

19 In the last year before this sentence, how many men did you have sex with? none
1
2-5
6-10
11 or more

20 Have you ever accepted money (or goods) for sex? yes
no

21 Have you ever paid for sex? yes
no

22 Have you ever been treated for a sexually transmitted disease? yes
no

23 Have you ever had anal sex with another man in prison? yes
no

Thank you for answering this confidential questionnaire.

ref: 93/010000/000000/000000

Pharmaceutical interventions

Highly Active Anti-Retroviral Therapy

(HAART): from expected survival of 10 years to 10 years **off** expected life-time.

Hepatitis B immunization: rapidly from **5%** of Scottish prisoners immunized to **over 60%** once HBV vaccine offered to all prisoners.

HCV therapies: sustained viral clearance rates!

Opiate Substitution Therapy: healthcare standard in Scottish prisons from 2003 . . .

Thank you, pharma . . .

Very well done!

But . . .

Still more to do.

Behavioural risk-factors for DRDs?

Unholy Trinity

Injecting

Misuse of alcohol

Misuse of benzodiazepines

NIQUAD cluster: NDTMS opiate-user cohort, 2005-2009 (Pierce et al.)

151,983 individuals in treated opiate sub-cohort & 442,950 person-years.

Covariate [K pys]	DRDs: & rate per 10K pys	Cox adjusted Hazard Ratio	95% CI
Male, 18-34 [153]	480 : 31	1.0 baseline	Interaction chisq on 2df = 16.5
Male, 35-44 [108]	463 : 43	1.36	1.20 – 1.55
Male, 45+ years [42]	219 : 52	1.73	1.47 – 2.03
Female, 18-34 [83]	128 : 15	0.51	0.42 – 0.62
Female, 35-44 [42]	145 : 35	1.17	0.97 – 1.40
Female, 45+ years [15]	64 : 43	1.48	1.14 – 1.93

Publication pending

Publication pending * 3

Naloxone (heroin antidote) on
release to reduce overdose deaths

**Drug-Related Deaths (DRDs)
soon after release: I**

Effectiveness on Trial: II

HMP Edinburgh

Overdose
deaths soon
after
prison-release

Seaman et al.



1. Seaman, Brettle & Gore: BMJ (1998)

Overdose deaths in 2 weeks after HIV injectors' releases from HMP Edinburgh [1983-94]

8 times higher than for comparable other fortnights at liberty ($p < 0.01$)

7 drug-related deaths, 6 from overdose.

2. Male index releases from Scottish prisons in July to Dec. 1996-99

Bird & Hutchinson: Addiction 2003

**Eligibility set by [B+H]
Applied by Scottish Prison Service
[SPS]**

male

aged 15-35 years on release
served 14+ days in prison
1st release in July-December
calendar years: 1996 to 1999

Drugs-related deaths in fortnight after prison: 19 486 male ex-prisoners, aged 15-35 years, released after 14+days' incarceration

DEATHS	1 st 2 weeks	subsequent 5 fortnights	RELATIVE RISK _(95% CI)
Drugs-related	34	23 (11 in 2 nd fortnight +12 in next 8 wks)	7 (3 to 16)
Other causes	3	18	0.8 (0.2 to 2.4)

WASH: 1 in 200 adult injectors
dead within 2 weeks after prison

*Judges
aware?*



Prison-based interventions



a) Information leaflet: how to avoid overdose risk after release

b) Naloxone on release: heroin antidote

UK's Advisory Council on the Misuse of Drugs: *advised in 2000 . . .*



Not until 2005

Naloxone
added to
UK's Exempt List
of
Prescription Only
Medicines
for administration by
anyone
in an emergency to
save life

Opioid Substitution Therapy in prisons: SPS's healthcare standard since 2002 "free petrol"

Graham, Fischbacher & Fraser: CSO-funded, linkage-study of Scottish prisoners' mortality, 1996-2007*.

Bird: Powerful enough* for **1996-2002** vs **2003-2007** comparison of Scotland's prison-based OST impact on:

- i) **12-week DRD-rate post-release:** no prior OST-decrease
- ii) **% of 12-week DRDs* in 1st fortnight:** prior based on Merrall et al. (2010): **60%** (B&H) vs **47%** (NSW).

Findings . . . ?

Publication pending

Internationally, 6 “major” studies meta-analysis

Merrall et al., 2010 Addiction Studies	DRDs: DRD rate per 1000 pys			1 st fortnight Relative Risk (95% CI)
	1 st fortnight	2 nd fortnight	next 8 weeks	
UK (E&W + Scotland)	92: 36	20: 8	42: 4	7.5 (5.7 to 9.9)
Australia (NSW & Western)	187: 24	64: 9	144: 5	4.0 (3.4 to 4.8)
USA (Washington State & New Mexico prisons)	27: 18	5: 4	10: 2	8.4 (5.0 to 14.2)
	8: 17	3: 6	10: 5	3.1 (1.3 to 7.1)

Naloxone, opioid antidote, is **POM** & given **IM**

1. By doctors & nurses
2. By ambulance paramedics
- 3. To prescribe:** by anyone to save life.
4. By authorised persons who come in contact with overdose victims & hold Naloxone for emergency-use: Scotland's Lord Advocate, 2011.
5. As Over-The-Counter Medicine in Italy Simini Lancet 1998; 352: 967.
6. **OTCM** advocated in USA by Kim, Irwin & Khoshnood Am. J. Public Health 2009; 99: 402-7 & in Australia by Lenton et al. Med. J. Aus. 2009; 191: 469.

Design assumptions: N-ALIVE

Eligibility: 18-44 years, history of heroin injection, 7+ days' incarceration.

- 1. At 80% of overdoses, some-one else is present**
- 2. 75% chance ex-prisoner carries Naloxone in 1st 4 weeks post-release; 50% chance in next 8 weeks**
- 3. 50% chance that Naloxone is administered by present other.**
 - ⇔ Effectiveness in 1st 4 weeks = 30%**
 - Effectiveness in weeks 5 to 12 = 20%**
- 4. 21st C: One overdose death in 1st 4 weeks per 200 ever-IDUs randomised to control group.**
- 5. Contamination . . .**

Prison-based, with-consent* **RCT** for 56,000 pre-release adult IDUs

Expected drugs deaths	1 st 4 weeks after release	Next 8 weeks after release
Controls [28,000 IDUs]	140	35
Naloxone [28,000 IDUs]	98	28



Prisoner's Informed consent to:

Intervention: Naloxone or control pack at release [overdose leaflet & prepaid reply card]

Confidential linkage to deaths register: [and to A&E non-fatal overdose admissions in PILOT]

Random assignment: blinded until release

Follow-up of recidivists (unique prisoner #):
via brief no-names self-Q

PILOT only: phone-call in 1st or 2nd fortnight after release for randomized **HALF** of consenters:
as **contact contaminates intervention!**



Prison-based pilot N-ALIVE Trial

MONTH	# Prisons	Monthly accrual	Cumulative accrual
Nov 2013	10	89	654
Dec 2013	10	72	726
Jan 2014	11	77	803
Feb 2014	15	67	870
Mar 2014	15	73	943
Apr 2014	15	102	1045
May 2014	15	85	1130
June 2014	15	82	1212

MHRN Networks & N-ALIVE Sites

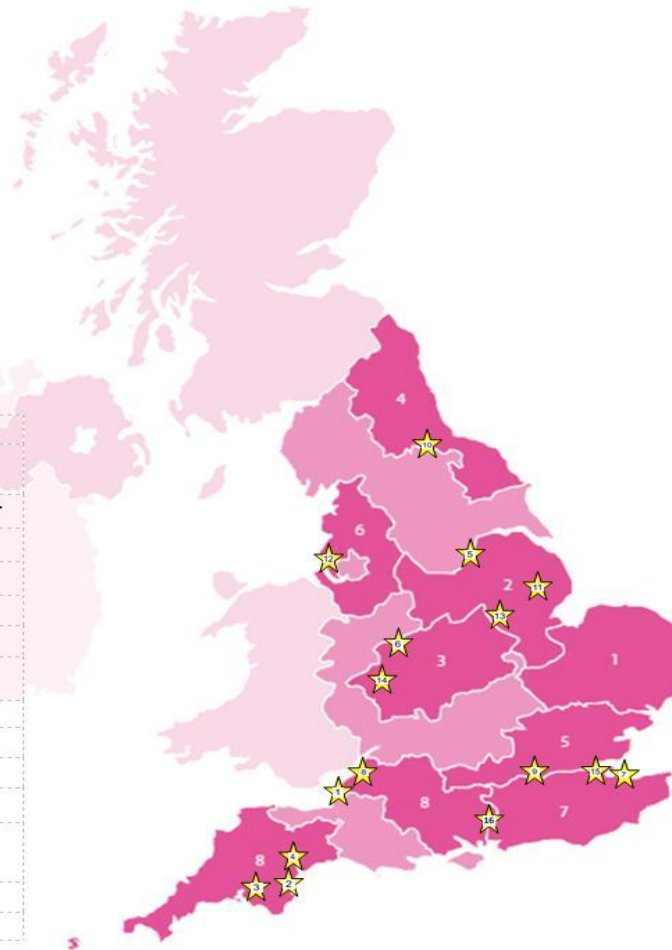
NIHR Mental Health Research Network (MHRN)

Mental Health Local Research Networks:

1. East Anglia
2. East Midlands
3. Heart of England
4. North East
5. North London
6. North West
7. South London and South East
8. West

For more information contact
mhrn@iop.kcl.ac.uk

- ### N-ALIVE Sites
- | | |
|----|--------------------------------|
| 1 | HMP Bristol |
| 2 | HMP Devon:
Channings Wood |
| 3 | HMP Devon: Dartmoor |
| 4 | HMP Devon: Exeter |
| 5 | HMP Doncaster |
| 6 | HMP Dovegate |
| 7 | HMP Elmley |
| 8 | HMP Gloucester
(Now Closed) |
| 9 | HMP Holloway |
| 10 | HMP Leeds |
| 11 | HMP Lincoln |
| 12 | HMP Liverpool |
| 13 | HMP Nottingham |
| 14 | HMP Oakwood |
| 15 | HMP Rochester |
| 16 | HMP Winchester |



Experimental vs Observational Methods to Determine:

Effectiveness of Naloxone-distribution
for reducing opioid overdose fatalities

Prison-based N-ALIVE Trial: England

Take-Home Naloxone Policy: Scotland

Scotland's Naloxone Policy: 2011-2013

Ministerial decision by Fergus Ewing + targets {1st year actual}

6,000 {**2,920**} take-home Naloxone-kits
+
5,000 { **730**} Naloxone-on-release-kits

N-ALIVE proposed national targets

8,000 {**20₉** * annual opioid-related deaths}

⇔ **One-third of current injectors . . .**

Scotland's monitoring: **NESI**

Needle Exchange Surveillance of Injectors:

NESI team interviewed 586 current IDUs in
July+August 2011

11% (63/586; 95% CI: 8% to 13%)
had been prescribed take-home Naloxone

Needle Exchange Surveillance of Injectors:

NESI team interviewed ~ 600 current IDUs in
July+August+September 2013

31% (95% CI: 27% to 35%) had been prescribed
take-home Naloxone in the past-year

Scotland

?

Primary outcome

Secondary outcome

NOT number of opioid-related deaths. **WHY?**

Scotland's rising tide of opioid-related DRDs: demography

Subgroup	female	MALES	MALES ONLY: by age at death			
			<25	25-34	35-44	45+ years
4 years of 2006-09: 1,994 DRDs (1,571 opioids)						
Opioids	280	1,291	211	490	418	172
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Scotland's outcomes: % opioid-related deaths (ORDs) with

Primary outcome:
4-week prison-release antecedent

Secondary outcome:
4-week prison-release or hospital-discharge
antecedent . . .

BASELINE:
Was **2007-2009**, now **2006-2010**
(**Primary outcome: 10% of 1970 ORDs**)

PRIOR EFFECT-SIZE of 20%-30% reduction:

10% down to 8% {5-years} **or 7%** {3-years}.

VALIDATION Scotland, 2006-2010: SDMD clients' DRDs after hospital discharge

Post-discharge	Person-years	DRDs 1996-2006	Rate per 1,000 pys	Pys	DRDs 2006-2010	Rate
Hospitalized	1697	125	74 (61- 88)	1497	75	50 (39-63)
Within 28 days after discharge	6714	165	25 (21- 29)	5556	125	23 (19-27)
29-90 days since discharge	10918	131	12 (10-14)	8903	107	12 (10-15)
91 days -1yr since discharge	32698	271	8 (7.3-9.3)	27306	235	9 (7.5-10)
1+ yrs since discharge	61446	259	4 (3.7-4.8)	82128	319	4 (3.5-4.3)
Never admitted	257643	458	1.8 (1.6-2.0)	209031	253	1.2 (1.1-1.4)

Publication pending

Ever-injectors' DRD risk in 1st 4-weeks after hospital-discharge: **2.4 DRDs** per 1,000 discharges.

Hospital-doctors

FAX to GP/drug tx.
team

CONSIDER
take-home Naloxone

**Public health policy
in Scotland &
Wales**



Quarter reduction in Scotland's % opiate-related DRDs within 4 weeks of **prison-release**

Design Considerations	Before %: 2007+08+09	% After THN: 2011+12+13	Statistical power
A priori Bird & Hutchinson, for 1996-99	200/1200 One in six	150/1200 {25% reduction}	85%
Oops . . . Best laid plans . . .	130/1240 One in ten	90/1200 {25% reduction}	58%
		{add 2014+2015} 150/2000	66%
BSU-inspired Solutions	i) Revise to before % within 4 weeks of prison-release or hospital-discharge; ii) Extend to 5-year baseline/after periods		

Scotland's **primary** & secondary outcomes

Scotland's ORDs with 4-week antecedents	Baseline: 2007+08+09 1247 opioid-DRDs		2006+Baseline+2010 1970 opioid-DRDs	
	Prison: %	Prison or Hospital: %	Prison: %	Prison or Hospital: %
All ages	134/1247: 10.8%	~ 20% <i>provisional</i>	193/1970: 9.8%	~ 20% <i>provisional</i>
Under 25	27/214: 13%		40/316: 13%	
25-34 years	60/445: 13%		86/724: 12%	
35-44 years	40/416: 10%		54/644: 8%	
45+ years	9/172: 5%		13/286: 5%	
THN2011			36/430 8.4%	
THN2012			22/399 5.5%	

Is it impact for RCT to be overtaken by policy it seeks to inform?

