FOCUS: Fluoxetine Or Control Under Supervision
Primary outcome and safety outcomes

Martin Dennis, on behalf of the FOCUS collaborators

The views expressed are those of the researchers and not necessarily those of the NHS, the NIHR or Department of Health and Social Care.

Background

- Fluoxetine has effects which might enhance recovery after stroke e.g. neuroplasticity in animal and imaging studies
- FLAME trial recruited 118 patients with ischaemic stroke to a double blind placebo controlled trial of 3 months of fluoxetine
- Fluoxetine associated with improvement in their primary outcome - Fugl Meyer motor score (p=0.003)
- Proportion with modified Rankin score (mRs) 0-2 increased from 9% to 26% (p=0.015)

Aims of FOCUS

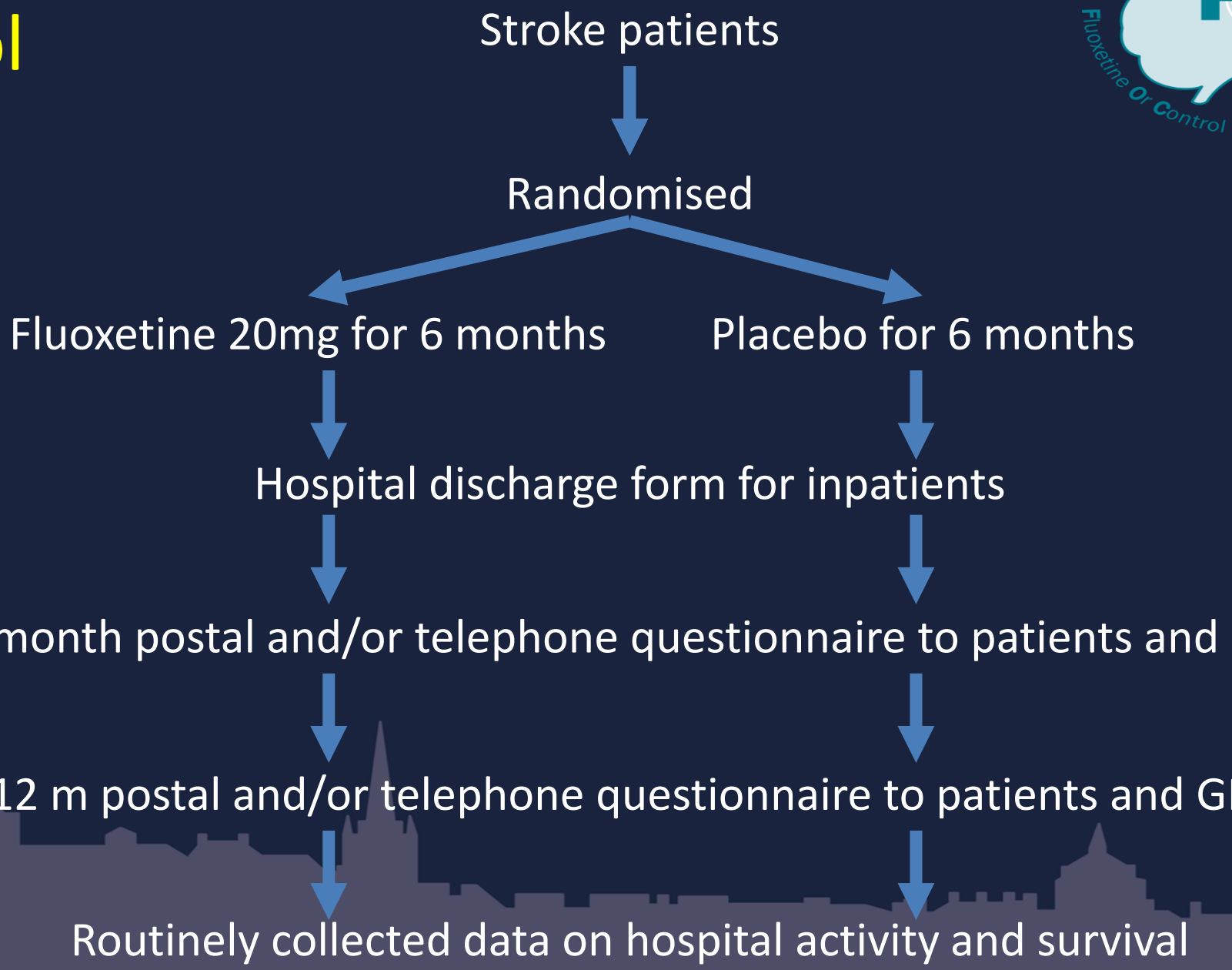
- Determine if fluoxetine 20mg daily for 6 months after stroke
  - Reduces dependency after stroke
  - Reduces other post-stroke problems
  - Whether any improvements persist to 12 months
- Provide robust evidence about benefits vs risks

FOCUS, AFFINITY and EFFECTs

- A family of three trials collaboratively designed
- Very similar protocols
- FOCUS (UK) aimed to recruit > 3000
- AFFINITY (Australasia & Vietnam) >1600
- EFFECTS (Sweden) >1500

- FOCUS is the first to report, the others continue to recruit

Protocol


Stroke patients
Randomised
Fluoxetine 20mg for 6 months
Placebo for 6 months
Hospital discharge form for inpatients
6 month postal and/or telephone questionnaire to patients and GPs
12 m postal and/or telephone questionnaire to patients and GPs
Routinely collected data on hospital activity and survival

Inclusion criteria

- Age ≥ 18 years
- Clinical diagnosis of stroke 2-15 days previously
- Brain imaging consistent with intracerebral haemorrhage or ischaemic stroke.
- Persisting focal neurological deficit present at the time of randomisation severe enough to warrant treatment from the patient's or carer's perspective

Exclusion criteria

- Stroke due to subarachnoid haemorrhage
- Received SSRI within last 5 weeks
- Epilepsy
- Medications with serious interactions with Fluoxetine
- Pregnant or breast-feeding
- Previous drug overdose or attempted suicide
- Participation in another Clinical Trial Involving a Medicinal Product (CTIMP)

Outcome measures

- Primary outcome: mRs at 6 months
- Safety: Adverse events within 6 months
- Secondary outcomes
  - mRs at 12 months
  - Stroke Impact Scale (SIS) at 6 & 12 months
  - Mental Heath Inventory (MHI-5) at 6 and 12 months
  - Fatigue (vitality score of SF-36)
  - Health related quality of life (EuroQol 5-D)
  - Survival to 12 months

Conduct

- 3127 patients recruited from 103 UK hospitals
  - Sept 2012 to March 2017
- Excellent balance in baseline characteristics between groups
- About 2/3 adhered fully to 6 months treatment
- Emergency unblinding performed in only 3 patients
- Primary outcome available in 99.3% at 6 months
- All analyses based on intention to treat

Result - Primary outcome

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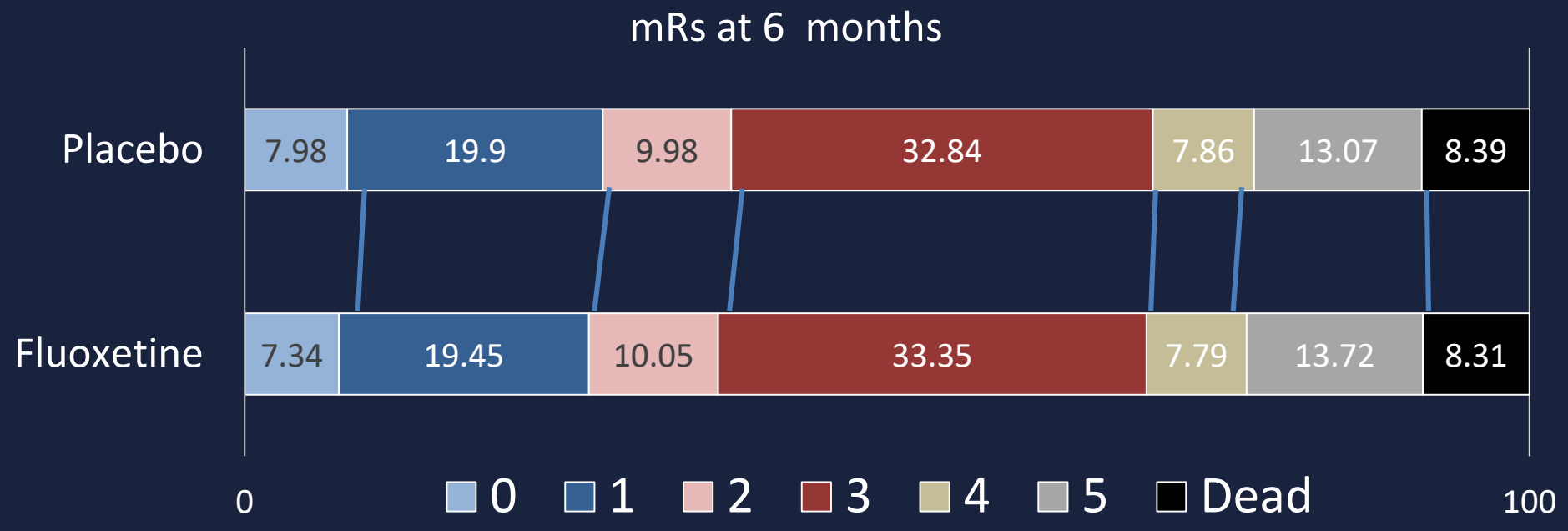

Common Odds Ratio = 0.951 (95% CI 0.839- 1.079; p=0.439)

Subgroup analyses

- No statistically significant interactions between treatment effect and subgroups:
  - Age
  - Stroke type (ischaemic vs haemorrhagic)
  - Stroke severity
  - Delay (2-8 vs 8-15 days)
  - Presence of motor dysfunction
  - Depression at baseline
  - Adherence to trial medication

Safety outcomes at 6 months

	Fluoxetine		Placebo		P value
Outcome event	n	%	n	%	
Epileptic seizures	58	3.7	40	2.6	0.0651
Fall with injury	120	7.7	94	6.0	0.0663
Fractured bone	**45**	**2.9**	**23**	**1.5**	**0.0070**
Hyponatraemia < 125mmol/l	22	1.4	14	0.9	0.1805
Hyperglycaemia	23	1.5	16	1.0	0.2602
Symptomatic hypoglycaemia	23	1.5	13	0.8	0.0940
New depression	**210**	**13.0**	**269**	**16.9**	**0.0033**
New antidepressant	**280**	**17.9**	**357**	**22.8**	**0.0006**
Attempted/actual suicide	3	0.2	2	0.1	0.6550

Safety outcomes at 6 months

	Fluoxetine		Placebo		P value
Outcome event	n	%	n	%	
Any stroke	56	3.6	64	4.1	0·454
Ischaemic stroke	43	2·8	45	2·9	0·826
Acute coronary events	15	1.0	23	1.47	0.191
Other thrombotic events	20	1.3	27	1.7	0.303
All thrombotic events	**78**	**5.0**	**92**	**5·9**	**0·268**
Haemorrhagic stroke	7	0·5	9	0·6	0·615
Upper gastrointestinal bleed	21	1.3	16	1.0	0.409
Other major bleeds	13	0.8	14	0.9	0.845
All bleeding events	***41***	***2·6***	***38***	***2·4***	***0·735***

Primary outcome and safety

- Fluoxetine did not improve the functional recovery (mRs) of stroke patients
- It reduced the risk of depression at 6 months
- However, increased risk of bone fractures

Further information

- These results will be in the Lancet today
- Participants will receive a newsletter including these results today along with their allocated treatment
- Gillian Mead my Co- chief investigator will present further results relating to secondary outcomes at 6 and 12 months in last plenary session
- We would like to acknowledge the input of our patients, their families, our collaborators, the research networks and our funders, the NIHR and Stroke Association