

Challenges in testing Fluoxetine in stroke patients

Experiences from the FOCUS trial

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Funders



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Outline

- Differences between FOCUS & EFFECTS
- Baseline data on first 1393 patients
- Adverse events up to 6 months
- Adherence to trial medication
- Successes
- Challenges

FOCUS, AFFINITY & EFFECTS

- Share common aims
- Share common protocol with only minor variations
- Chief Investigators participate in all three trials
- Data monitoring committees able to share data/experience
- Aim to publish a combined individual patient data meta-analysis of 6000 patients

Differences from EFFECTS

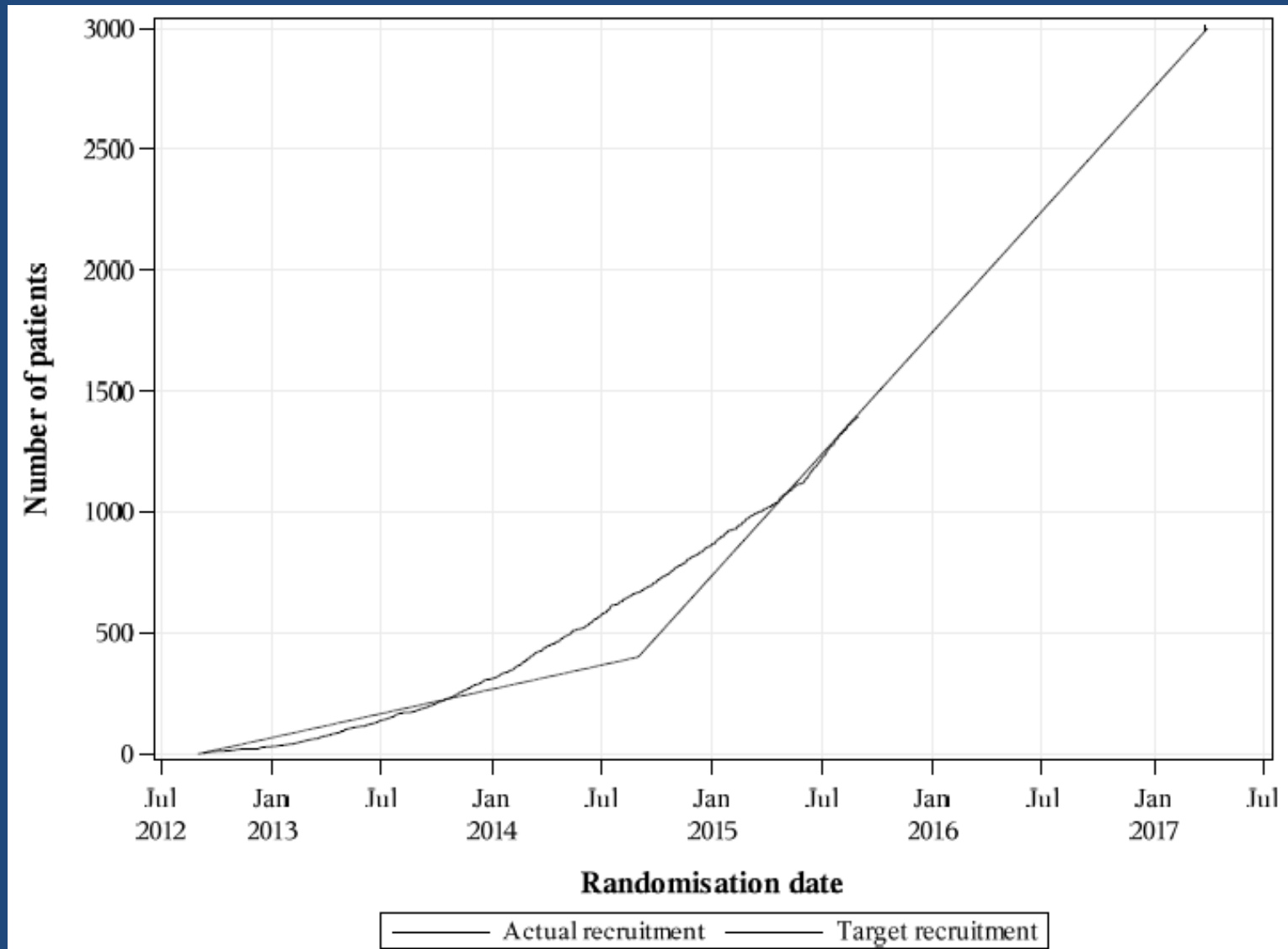
- We allow consent from family etc
- We collect patient/family contact details at baseline
- We dispense one bottle with 186 capsules
- Centres have research nurses provided by NHS funded Research Networks
- Our centres take no part in follow up after discharge – no face to face assessments
- We do not collect SF12, MADRS, DSM-IV
- Target recruitment 3000



Recruitment so far

- Recruitment started September 2012
- So far 1500 patients recruited from 81 centres (some of which have become 'live' over the last few months)
- Aim to recruit 3000 in total by April 2017
 - Recruitment rate of 100 per month from 120 centres

Recruitment



Adherence to Investigational Medicinal Product (IMP)

- No gold standard method
- Adherence recorded during hospital admission (medication chart review)
- Reported date of temporary/permanent stopping
- Adherence at 6 months
 - patient reported (various questions)
- Counts of capsules returned

Some measures of adherence

- 92/1192 (8%) not taking IMP at hospital discharge
- 224/849 (26%) reported did not complete 6 month
- Median duration of treatment
 - 186 days (IQR 163-186)
- Median duration in those not completing course
 - 58 days (IQR 25 to 103)

Successes

- Shared protocol agreed between FOCUS, AFFINITY & EFFECTS – published in IJS 2015
- Government funding obtained for main phases of all three trials
- Overcame regulatory issues to initiate all trials

Successes

- Procurement of Fluoxetine/Placebo
 - UNICHEM manufacture both in GOA
 - Imported via Niche Generics (Oxford)
 - Purchased via Discovery Pharmaceuticals
 - Delivered to SHARP for packaging/labelling/storage & distribution
 - Same as for EFFECTS



IT systems

- Although slow to develop now provide:
 - Web based training and testing for centres
 - Support for regulatory processes
 - Web based randomisation
 - Stock control for trial drug
 - Data entry for follow up
 - Centre alerts
 - Housekeeping more complicated – still waiting for ultimate system
- } Shared with EFFECTS

Recruitment

- Continue to enrol new centres – aiming for >120
- Encourage active centres
 - Newsletters – performance tables
 - Monthly prizes for best performers
 - Centre visits
 - 24/7 helpline support
- Minimise burden on centres

Early stopping of IMP

- Patients change their minds
 - Insufficient explanation
 - Insufficient time to consider
 - Lack of involvement of relatives
- Adverse effects
 - Relatively uncommon
 - Look for alternative explanations
 - Use temporary (1 week) stops and restarts to establish causation

Withdrawal

Patients can withdraw consent from the trial without giving a reason at any time

- Stopping the IMP
 - Emphasise still want to follow up
- Not wanting patient to be disturbed by follow up
 - OK to follow up via relatives?
- Patient & family not to be bothered
 - OK to follow up via family doctor?
 - OK to follow up via routine mortality/hospital data?

Withdrawal

- Local investigators and central team need to define precisely what the patient wants
 - Stop IMP only
 - Not to receive questionnaires etc
 - Not to have family involved
 - Not to have GP providing data
 - Not to have routine data accessed
 - Complete withdrawal of consent – but we can use all data collected up to that point!

Some reasons for poor adherence

- Dispensing the wrong bottle of IMP
- Losing the IMP on ward
- Failures to send IMP home with patient
- Losing IMP or trial awareness during moves between wards and hospitals
- Describing IMP as “Fluoxetine” in discharge letter to GP
- Pharmacy provided dosette boxes only contain meds prescribed by GP
- GPs prescribing Fluoxetine

Problems and responses

- Wrong bottle dispensed
 - Encourage careful checking in centre
 - Check confirmation of dispensing fax matches allocation
 - Rapid identification and correction
- Patient must receive allocated treatment (Fluoxetine or placebo) and will be analysed by allocation (intention to treat) – not necessarily the allocated treatment number

Problems and responses

REGULAR MEDICATIONS											
YEAR										DATE & MONTH	
VARIABLE DOSE MEDICATION Date Medication (Print Generic Name) Drug level When level taken											
Route Frequency Dose Prescriber to enter dose times and individual doses Prescriber											
Indication Pharmacy Time to be given: Prescriber Signature (Print Your Name) Contact Time given											
WARFARIN (Marevan/Coumadin) Route Prescriber to enter individual doses Target INR Range INR Result Prescriber to enter individual doses Prescriber											
Indication Pharmacy I600 (Name 1) Prescriber Signature (Print Your Name) Contact Nurse 2											
DOCTORS MUST ENTER administration times											
Date Medication (Print Generic Name)											
Route Dose Frequency & Enter Times											
Indication Pharmacy											
Prescriber Signature (Print Your Name) Contact											
Date Medication (Print Generic Name)											
Route Dose Frequency & Enter Times											
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Prescriber Signature (Print Your Name) Contact											
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Prescriber Signature (Print Your Name) Contact											
Date Medication (Print Generic Name)											
Route Dose Frequency & Enter Times											
Indication Pharmacy											
Prescriber Signature (Print Your Name) Contact											
Clinical Pharmacist Review:											

- Losing the IMP on ward
 - Train ward staff about trial
 - Involve patients and families
 - Resupply if necessary – we have a system for this
- Describing IMP as “Fluoxetine” in discharge letter to GP
 - Ensure described properly during admission on medication chart (FOCUS trial medication (Fluoxetine or Placebo))
 - Find out how IMP can be described in your local electronic prescribing system
 - Train those prescribing discharge drugs
 - Pharmacy to check discharge prescription is correct

Problems and responses

- Failures to send IMP home or to downstream unit with patient
 - Train stroke unit staff
 - Discharge checklist
 - Education & information for downstream units
 - Phone patient shortly after discharge to check
 - Encourage patients/families to query and use helpline
 - Resupply promptly if missing

Dosette boxes

- In UK many patients receive their prescribed medication in dosette boxes provided by local pharmacy
- Currently no way of getting the trial medication included
- Have to rely on patients/family/carers



Prescription of SSRIs

- Mistakes by discharging doctor and GPs
 - Incomplete or misleading information on discharge letter
 - GPs don't read letters carefully
- Failure to read information or adhere to guidance about treatment of depression in trial
 - Mirtazapine
 - Trazadone
 - Tricyclics

Actions to reduce inappropriate prescription of SSRIs

- Education of stroke unit staff
- Educate patients/carers – encourage them to ring helpline if concerned
- Encouraging real time reporting of depression via helpline so treatment discussed
- Revision of initial information to GPs
- Additional “safety alert” letter sent to GPs after discharge (but depends on prompt completing of discharge forms!)

Requests for unblinding

- All assessed by chief investigator
- Reasons for request varied
 - Curiosity
 - Adverse effects
 - Overdose
- Only one patient unblinded so far because answer would make a significant difference to management
- Trial team remain blinded to allocation

Follow up

- Response to postal questionnaire lower than in FOOD, CLOTS – about 80%. In FOCUS only 50-60% complete
- We do not use routine postal reminders because of inevitable delays
- CIs phone non responders to encourage response or more often answer over phone
- Very time consuming

Follow up

- Incomplete/incorrect contact information provided at randomisation/hospital discharge
- GPs filing but not reading information sent out about trial
- GPs not identifying that we have sent them a copy of the consent form already
- Teams not clarifying with patients that follow up still important even when IMP stopped early

Outcome measures at 6/12 and 12/12

- mRS – simplified modified Rankin questionnaire (5 qs)
- EuroQol -EQ5D-5L (5 qs)
- SF36 – vitality subscale (4 qs)
- Mental Health Inventory (MHI 5)(5 qs)
- Stroke Impact Scale (SIS) - 59q!
 - Limb strength (4q)
 - Memory & thinking (7q)
 - Emotion (9q)
 - Communication (7q)
 - Daily activities (11q)
 - Mobility (9q)
 - Hand function (4q)
 - Limitation of participation (8q)
 - Overall recovery (Visual analogue scale)

Important

- Screen for incompatible answers before entering data
 - mRs questions
 - SIS
 - Miss items by mistake
 - Don't read questions properly
 - Don't answer those which don't seem relevant
- Query incompatible answers by phone

Simplified modified Rankin questionnaire

7. If you had to, could you live alone without any help from another person? (This means being able to bathe, use the toilet, shop, prepare or get meals, and manage finances) **Yes** **No**
8. Can you do everything that you were doing right before your stroke? (even if slower and not as much) **Yes** **No**
9. Are you completely back to the way you were right before your stroke? **Yes** **No**
10. Can you walk from one room to another without help from another person? **Yes** **No**
11. Can you sit up in bed without any help? **Yes** **No**

SIS Emotion

In the past week, how often did you....	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a) Feel sad?	5	4	3	2	1
b) Feel that there is nobody you are close to?	5	4	3	2	1
c) Feel that you are a burden to others?	5	4	3	2	1
d) Feel that you have nothing to look forward to?	5	4	3	2	1
e) Blame yourself for mistakes that you made?	5	4	3	2	1
f) Enjoy things as much as ever?	5	4	3	2	1
g) Feel quite nervous?	5	4	3	2	1
h) Feel that life is worth living?	5	4	3	2	1
i) Smile and laugh at least once a day?	5	4	3	2	1

Questions?