

# FOR-DMD – FOR YOU!

Newsletter 1 – 15<sup>th</sup> February 2013



Welcome to the first FOR-DMD trial newsletter. We intend to keep you up to date with progress of the trial, to provide you with hints on study procedures and to document answers to your frequently asked questions. If you have suggestions for future newsletters, please email us at [for.dmd@newcastle.ac.uk](mailto:for.dmd@newcastle.ac.uk), with NEWSLETTER in the subject line of your message.

*Elaine McColl, FOR-DMD newsletter editor, on behalf of the FOR-DMD steering group*

## A Message from the Chief Investigators

After several years in set up, the FOR-DMD study is finally recruiting and sites are being activated on a daily basis. We are very excited to see this trial get off the ground and need to share our thanks to all of those involved to date who have worked very hard to solve the problems (foreseen and not) with setting up such a large and complex study. With recent papers highlighting the continued discrepancies in the use of steroids, we remain convinced that the only way to get an unbiased view of the relative risks and benefits of the various steroid regimes in current use is to embark on a randomised study. We are very pleased that you as participating sites have stayed with us during this process and that you too remain committed to this aim. The next phase of the study is in your hands, with a real need to get boys recruited quickly in order to meet our targets and finish the study in a timely manner! These questions need answering and we believe that we have set up a good study to address them.

The study team remains at your disposal to answer questions and resolve any problems. You can reach us at [for.dmd@newcastle.ac.uk](mailto:for.dmd@newcastle.ac.uk)

Thanks for being a key part of the FOR DMD team!

*Katie Bushby and Berch Griggs, FOR-DMD Chief Investigators*

## Trial Registration

The FOR-DMD trial is now registered with clinicaltrials.gov (<http://www.clinicaltrials.gov> – Identifier NCT01603407) and current controlled trials (<http://controlled-trials.com> – ISRCTN identifier 46102316).



## Visit the FOR-DMD Website

<http://for-dmd.org> is the study website for patients, families and site staff. Here you will find the full list of participating sites, study team contact details and a summary of the trial. The FOR-DMD newsletters and FAQs are also available from this site. There is also a selection of games and puzzles to entertain study participants during their visits.

Please visit the website and let us know what you think of it; there's a link there for making contact with the study team.

The QR tag below can be used to navigate directly to the website.



## Study Approvals



In the US, FOR-DMD received its IND from the FDA on 29<sup>th</sup> October 2012. The FDA included some questions/comments in their approval notice and these were addressed to the FDA's satisfaction on 2<sup>nd</sup> January 2013. University of Rochester received approval as the study coordinating centre on 23<sup>rd</sup> October 2012.



In Canada, FOR-DMD received Health Canada approval on 4<sup>th</sup> January 2013.



In the UK, favourable ethical opinion was confirmed by NRES Committee South Central – Southampton B Research Ethics Committee on 24<sup>th</sup> January 2012. Clinical trial authorisation was obtained from the MHRA on 12<sup>th</sup> November 2012. Central sign-off for R&D approval was obtained on 7<sup>th</sup> December 2012.



In Germany, the lead Research Ethics Committee (Freiburg) has reviewed the FOR-DMD study after consultation with all local Ethics committees of participating sites. Small changes have been requested; the Freiburg team have these in hand, and favourable opinion is expected shortly. A response from the competent authority BfArM is expected by the end of February. The model sponsor-site clinical trial agreement has been provided to all sites for review.



In Italy, Research Ethics Committee approval ("single opinion") was received at the coordinating centre (Padova) at the end of December 2012; the document has been shared with all other Italian sites to be evaluated by their local RECs, with review scheduled at varying dates to end of February. The favourable ethical opinion from the coordinating centre was received at the Italian Medicine Agency (AIFA) on 28<sup>th</sup> December 2012. The model sponsor-site clinical trial agreement has been provided to all sites for review.

## Site Activation and Subject Screening & Recruitment

As of 14<sup>th</sup> February 2013, a total of 13 sites – 10 in the US, 1 in Canada and 2 in the UK – have been activated and are open to subject screening and recruitment. Many other sites in these three countries are very close to activation, as shown in the dashboards below; a green circle denotes that the required action has been completed, a yellow circle that the action is near to completion and a red circle that action is yet to be completed. We anticipate German and Italian sites to start coming on board from March, once all approvals in these countries are in place.

Also as of 14<sup>th</sup> February, a total of five boys have been identified and screened, two in the US, two in the UK and one in Canada. One boy has been randomised, at Dr Jean Mah's site in Calgary. **This first randomization took place on 30<sup>th</sup> January 2013. This date starts the clock for the two year recruitment window – 713 days to go!** Can all open sites please keep us updated about their screening plans and progress!



Congratulations to Dr Shieh (site PI), Angel Hu (TC), and their colleagues at UCLA, the first US site and the first site overall to be activated, on 3<sup>rd</sup> January 2013. UCLA was also the first US site to screen, on 16<sup>th</sup> January 2013.



Congratulations to Dr Mah and colleagues at Calgary, the first Canadian site to be activated, on 14<sup>th</sup> January 2013. Special congratulations to Dr Mah and colleagues on being the very first site to randomise a patient on 30<sup>th</sup> January 2013.



Congratulations to Professor Straub and colleagues at Newcastle upon Tyne, the first UK site to be activated, on 12<sup>th</sup> January 2013. Newcastle was also the first UK site to screen, on 28<sup>th</sup> January 2012.

SITE	REGISTERED IN "SAM"	SUBMITTED SSI	SIGNED CLINICAL TRIAL AGREEMENT	R & D APPROVAL	SITE INITIATION FORM	ACTIVATED FOR RECRUITMENT
NEWCASTLE	●	●	●	●	●	●
ALDER HEY	●	●	●	●	●	●
BIRMINGHAM HEARTLANDS	●	●	●	●	●	●
OXFORD CHILDREN'S HOSPITAL	●	●	●	●	●	●
EVELINA CHILDREN'S HOSPITAL	●	●	●	●	●	●
GREAT ORMOND STREET (GOSH)	●	●	●	●	●	●
LEEDS TEACHING HOSPITAL	●	●	●	●	●	●
YORKHILL HOSPITAL (GLASGOW)	●	●	●	●	●	●
ROYAL MANCHESTER	●	●	●	●	●	●
UNIVERSITY HOSPITAL WALES	●	●	●	●	●	●

SITE	REGISTERED IN "SAM"	SIGNED SUB-AGREEMENT	LOCAL ETHICS APPROVAL	SITE INITIATION FORM	ACTIVATED FOR RECRUITMENT
<b>USA</b>					
UNIVERSITY OF ROCHESTER MEDICAL CENTER	●	●	●	●	●
LURIE CHILDREN'S HOSPITAL (CHICAGO)	●	●	●	●	●
KANSAS UNIVERSITY MEDICAL CENTER	●	●	●	●	●
KENNEDY KRIEGER INSTITUTE (MARYLAND)	●	●	●	●	●
NEMOURS CHILDREN'S HOSPITAL (FLORIDA)	●	●	●	●	●
NATIONWIDE CHILDREN'S HOSPITAL (OHIO)	●	●	●	●	●
PENN STATE HERSHEY CHILDREN'S HOSPITAL	●	●	●	●	●
SUNY DOWNSTATE MEDICAL CENTER (NEW YORK)	●	●	●	●	●
UC DAVIS (SACRAMENTO)	●	●	●	●	●
UCLA	●	●	●	●	●
UNIVERSITY OF NEW MEXICO	●	●	●	●	●
UNIV. OF TEXAS SOUTHWESTERN MEDICAL CENTER	●	●	●	●	●
VANDERBILT CHILDREN'S HOSPITAL	●	●	●	●	●
BOSTON CHILDREN'S HOSPITAL	●	●	●	●	●
<b>CANADA</b>					
LONDON HEALTH SCIENCES CENTRE (ONTARIO)	●	●	●	●	●
ALBERTA CHILDREN'S HOSPITAL (CALGARY)	●	●	●	●	●
HEALTH SCIENCES WINNIPEG (MANITOBA)	●	●	●	●	●

## UPDATES, HINTS AND FAQs

### **TRAINING AND SITE ACTIVATION**

Video and Powerpoint presentations from the FOR DMD US Investigator Meeting (IM) are available on Chillibean. They are divided by study role (Principal (Site) Investigator, Trial Coordinator and Clinical Evaluator).

Study staff who have attended an IM (in Rochester or Newcastle) are not required to review the video but can use them as a refresher, if they think it might be useful.

As part of the study mandatory training, any study staff member who did not attend an investigator meeting is required to review the Powerpoint presentations and accompanying video(s) listed under their study role before performing any study procedure. This needs to be documented on the training form, which then should be signed by the site PI to confirm the completed training. Signed forms need to be returned to Kim Hart (via fax or email, contact details in section 2.1 of the MOO) to allow site activation.

If a primary or back-up Clinical Evaluator did not attend an Investigator Meeting, they should check with Michelle Eagle (UK/EU sites) and Wendy King (US/CAN sites) (contact details in the Clinical Evaluator Manual, section 5) to determine what type of training is required.

### **EXPeRT**

#### **Connectivity problems**

We have encountered some connection problems with PCs running multiple Internet Explorer (IE) sessions when logging in to EXPeRT, and also on PCs that have other browsers installed (Google Chrome and Firefox, for example). In addition to previous recommendations noted (IBM compatible PC; Internet Explorer (IE) 6 or higher; no toolbars loaded; pop-up blockers disabled), if you experience problems accessing EXPeRT through IE please try the following:

- Close other IE tabs (if any are open) and run EXPeRT alone
- If you have Google Chrome or other non-IE browsers installed (even if not actively running them) try running on a PC without these browsers installed
- If you still experience problems contact the MSG-CC help desk ([FOR-DMD-Help@urmc.rochester.edu](mailto:FOR-DMD-Help@urmc.rochester.edu))

#### **EXPeRT data entry**

When you want to add a subject on EXPeRT, a drop-down box will ask you to enter the site country. The system will offer you only the US and UK as options (but not Canada, Italy or Germany). Please note that, regardless of where your site is located, you do NOT need to complete this field (i.e. do not need to make a selection in the drop-down box). Instead, the country will be automatically captured via the subject ID number.

In that same screen ('add a patient'), there is a field for baseline visit date. Please note that this field does not need to be completed either, as the baseline visit date will be automatically captured on CRF01.

### **PHYSIO ASSESSMENT**

The physio assessment should be performed without parents present in the room. However we understand that when a child is very immature and is new to the study and staff this might be difficult. Therefore if it is not possible to gain cooperation from the child at the screening visit it is acceptable to allow the parent to stay in the room so long as they do not interfere with the assessment. On the next visit (Baseline) when the boy is more familiar with the staff, the environment and study procedures we would hope that the parent can remain outside. The requirement for this adaptation to the manual need to be determined at the discretion of the study staff on a case by case basis.

Of priority is to get a good assessment without parental influence. Please contact Michelle Eagle or Wendy King if you have any questions about this (contact details in the Clinical Evaluator Manual, section 5).

## **Video techniques**

It is best to use a tripod when videoing the assessment. Do not worry about getting the perfect video. It is more important to get a good assessment. If there are two site staff available, then one person can take care of the videos leaving the evaluator to concentrate on the assessment.

## **FVC recording on CRFs**

In order to accommodate the changes to the FVC reproducibility eligibility criterion we have modified EXPeRT to allow for capture of both FVC testing sessions at the screening visit. When filling out the paper FVC form (CRF50) please be sure to include the correct time for each testing session, which will allow us to keep track of the data later. Enter each session as a separate eCRF50 in EXPeRT. To add a second record, click the '+' sign in the upper right hand corner of the screen. See page 14 of the EXPeRT User Guide v 1.3 (Adding a Record) for more information. This will allow us to document that the percent variability was calculated correctly.

## ***SCREENING, RANDOMIZATION AND STUDY DRUG ORDERING***

### **Screening log – CRF00**

- CRF00 will be used to monitor screening at each site and must be filled out on the paper form **and** electronic form (eCRF)
- Paper CRF00 can be downloaded and printed from EXPeRT (from the document sharing folders in EXPeRT, lower right quadrant, under CRFs).
- On the paper form, sites can write in all the subjects who have been screened at that site as one continuous log, so they all can be seen at a glance.
- On the eCRF, however, each subject will just have their own individual one line CRF00 into which to enter the data.
- To see eCRF00 on EXPeRT, the subject has to be created first (see EXPeRT guide for details). Once the subject has been created, eCRF00 will appear automatically, together with all other screening visit forms.

### **Subject screening numbering**

- Subjects should be numbered sequentially as they are considered for screening (pre-screened). For example, USA12S01, USA12S02, USA12S03 etc. If the subject failed screening (e.g. refused to take part in the study, failed eligibility criteria), he will nonetheless maintain this sequential screening number. Therefore the first subject randomized at the site might not be subject 01.
- Please note that if and when a subject is screened and subsequently successfully randomized the 'S' in position 6 of their ID will change to an 'R' to reflect this. The system will do that for you automatically, so you don't need to worry about doing that yourself.

## Randomisation

Randomization will be notified via email (see MOO, section 3.2.3, page 18).

- The randomization notification process has been configured to include the site principal investigator, primary trial coordinator, and secondary coordinators (if there are any and their inclusion has been previously requested by the site ) and the person designated as 'study drug recipient' into the email.
- **Unfortunately, the system has now been finalized and we will therefore not be able to add any additional addresses beyond those listed above.**
- Nonetheless there are some options that can be explored if you would like to add additional people to receive the notifications, such as auto-forwarding in your email system. Please contact Bill Martens (contact details provided in the MOO, section 2.1, page 8) if you need any assistance with this.
- Remember that the site investigator has to sign off on the screening visit (i.e. has to sign eCRF01) in order to randomize, and that the notifications will be generated within an hour or two of randomization. Therefore, do not complete a randomization when notifications would arrive while the site investigator or primary trial coordinator is on leave (given the speed of notification and the need for the site investigator to sign off, this is an unlikely scenario).

## Study drug ordering and shipment (eCRF11)

- Date of study drug shipment to the site needs to be reported and recorded on eCRF11.
- If the study drug is shipped directly to the site investigator or to the primary trial coordinator, the recipient will be able to enter date of shipment into the eCRF11.
- For sites where study drug will be shipped to their pharmacy, they will need to agree with their pharmacy how to confirm shipment. (e.g. the pharmacy could notify the primary trial coordinator that the shipment has been received, and the coordinator can then update CRF11 in EXPeRT). Please contact Bill Martens if you have any questions about this process, including the option of having a member of pharmacy staff confirm receipt.

## SCREENING VISIT AND INVESTIGATIONS

Please note that all screening study procedures should be performed only after written informed consent from the parent(s) (and assent from the child, if required) has been obtained.

**Q: If a subject recently had an investigation which is part of screening procedures (e.g. Echocardiogram), does it need to be repeated?**

**A:** This will depend on the investigation (e.g. blood tests must be performed at screening), the time window since the investigation and technique. Please contact the Chief Medical Coordinator (Dr Michela Guglieri, contact details in section 2.1 of the MOO) to discuss the specific circumstance.

**Q: Does the order in which we perform the tests matter?**

**A:** At screening we would recommend checking the reliability of the FVC and the ability to take tablets first as these are inclusion criteria. If the boy does not pass these inclusion criteria, the family can be provided with placebo tablets and FVC filters/tubes to practice at home and re-screening should be considered. However if the boy is not able to provide reliable FVC measures and/or to swallow tablets, sites can consider not proceeding to the other screening procedures on that day. Physio assessments have a specific order in which the tests should be performed (see Clinical Evaluator Manual, section 3, page 9). This applies at screening and at each follow up visit. Otherwise, the other study procedures can be performed in the order that it is most convenient for the subject and/or study staff.

**Q: Can tablets be swallowed with yogurt or any other liquid/food?**

**A: Yes.** As previously discussed, we are aware that the ability to swallow tablets will be one of the major difficulties for young children. As per common recommendation from medicines for children, tablets should be swallowed with a glass of water, milk or juice. Alternatively, they can be concealed in a small amount of soft food such as yogurt, applesauce, honey or jam. If tablets are to be concealed in this way, we suggest that you discuss with parents what the child would manage best, and whether it would be better for the child to see the tablets before concealment. **Tablets should not be chewed or crushed.**

**Q: Do we only do the second FVC at the screen visit?**

**A:** Yes, The FVC re-test needs to be done at screening day one only to confirm eligibility

**Q: Can the subject's medical and medication history be collected from the subject's medical notes?**

**A:** Yes. However it is important that the information are confirmed with the family at the study visit. Please note also that CRFs should not be pre-filled with subject information until the informed consent form (and assent if required) is signed.

**Q: Can blood samples for bone-metabolites and for bio-banking be collected at screening together with the other blood samples?**

**A:** We are aware that blood sample collection might be stressful for young children. As per protocol blood samples for bone-biomarkers and for biobanking have to be collected at baseline. Collection of these samples at screening would represent a deviation from the protocol and would therefore require the site Investigator to complete a deviation form (eCRF80 see section 6.6 of the MOO, page 48). However please note that in line with GCP and paediatric guidelines in research, you are not allowed to collect more than 1-1.5 ml/kg within 24 hours for research studies in paediatric population.

The urine sample for bone-DMD needs to be collected at baseline as families will need to be instructed to collect the 2 hour morning sample (see MO, section 6.10.2.20 page 61 for details) and no study procedures can be performed before consent.

**Q: How involved is the eye exam? Can the site investigator do this or should we schedule an eye appointment?**

**A:** The eye check needs to be performed by an ophthalmologist or a qualified eye care practitioner (see section 6.13 of the MOO)

**Q: Will the DEXA scan be centrally read and will sites receive DEXA scan result reports?**

**A:** No, the DEXA scan will be sent centrally (ML Bianchi) for quality control only. The DEXA scan will therefore need to be interpreted locally and interventions should be arranged as per local clinical guidelines (see MOO, section 6.14.4, page 66).

**Q: What is the wrist X-Ray for?**

**A:** The wrist X-Ray is being performed for bone age calculation. This might not be a standard procedure at the radiology department; therefore please ensure that "wrist X-Ray for BONE AGE" is specified on the requisition form