How to go around conducting a clinical trial in small populations: Duchenne muscular dystrophy

CTs in rare diseases London 30th November 2015

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The JWMDRC

- The John Walton Muscular Dystrophy Research Centre (JWMDRC) at Newcastle has a particular interest in translational research in rare genetic neuromuscular diseases
- We been involved in protocol writing and review, and conduct of several phase I, II and III clinical trials in Duchenne muscular dystrophy (DMD) and other neuromuscular condition.
- The JWMDRC provides the secretariat for the TREAT-NMD alliance committee

Duchenne Muscular Dystrophy (DMD)

- DMD is a rare genetic neuromuscular diseases with a birth incidence worldwide of 1 in 5,000 live male births.
- It is an X-linked recessive disorder, affecting almost exclusively boys
- Mutations in the dystrophin gene are responsible for the disease, and include deletions, duplications and point mutations.
- Over the last years, new and promising experimental approaches have been developed to find possible curative treatments, particularly focusing on the correction of the genetic defect that cause the disease.

Clinical trials in Duchenne muscular dystrophy

- Limited number of patients
- Limited number of specialised centres
- Variability of the care standards

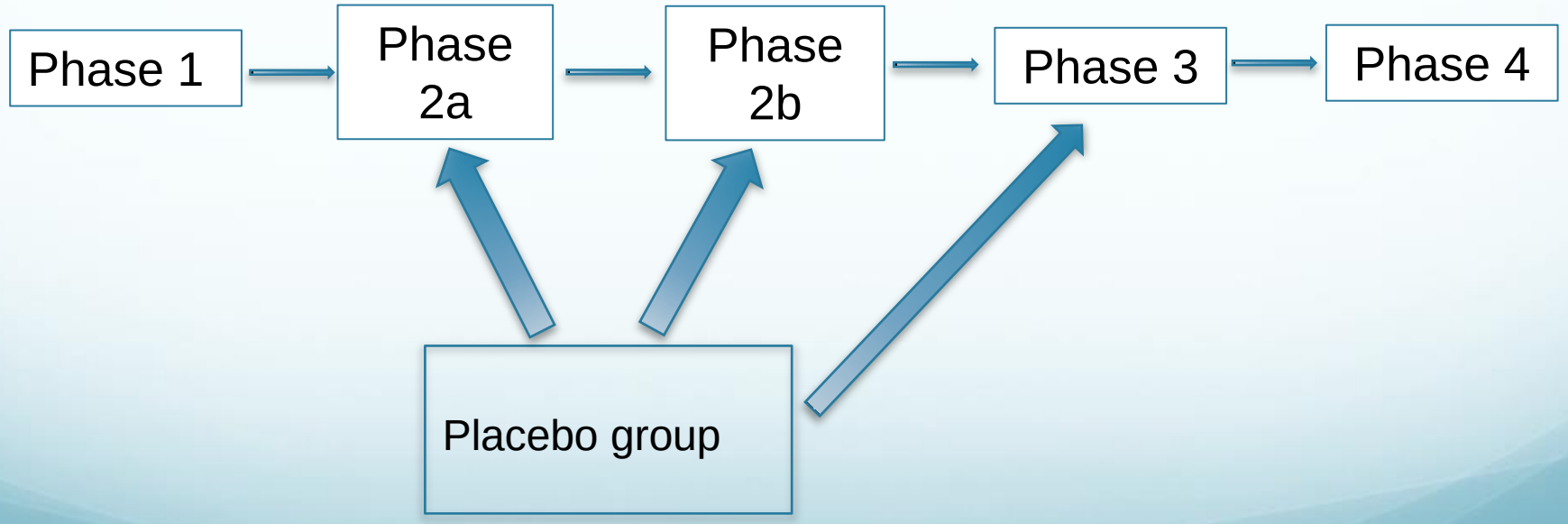
Clinical trials in Duchenne muscular dystrophy

- Limited number of patients
  - Rare disease
  - Mutation specific approaches
  - Subgroup studies

Patient registries

Clinical trials in Duchenne muscular dystrophy

Drug development programme



Clinical trials in Duchenne muscular dystrophy

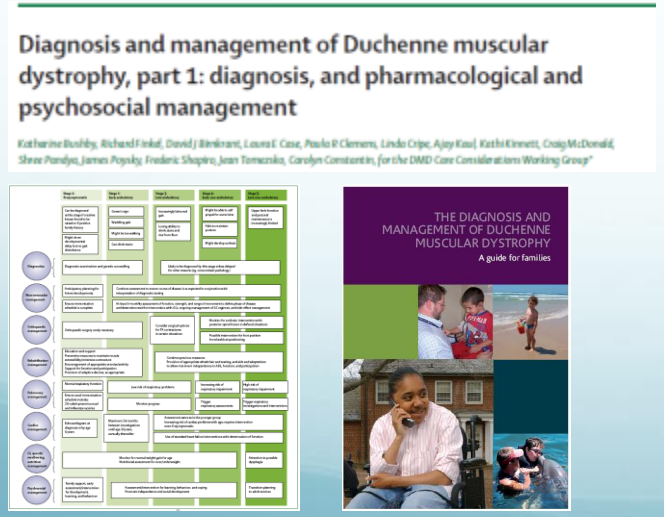
- Limited number of specialised centres
  - ➢Multi-centre, international trials
- Diversity in law and regulatory requirements among different countries

Care and Trial Site Registry

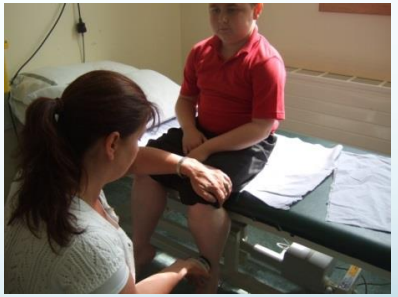
Clinical trials in Duchenne muscular dystrophy

- Variability of care standards

Standards of Care

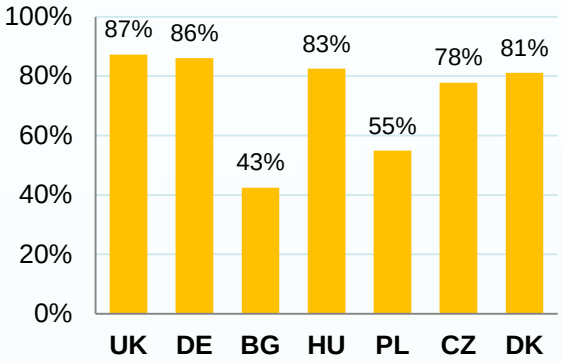


Outcome measures

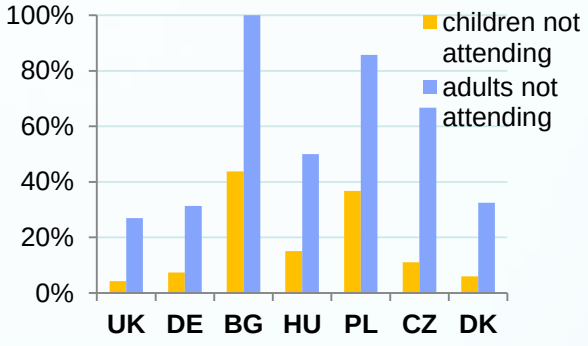


Clinical trials in DMD

Attendance NM Centre

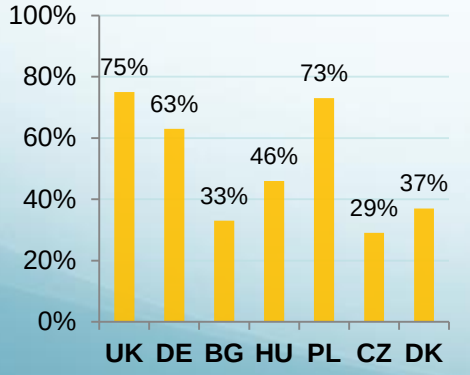


Attending NM centre at least once/year

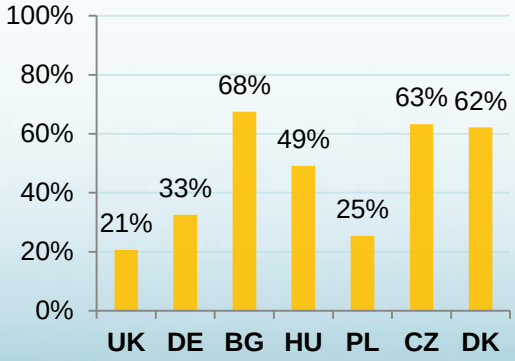


Patients **not** attending NM centre at least once/yr

Steroid use

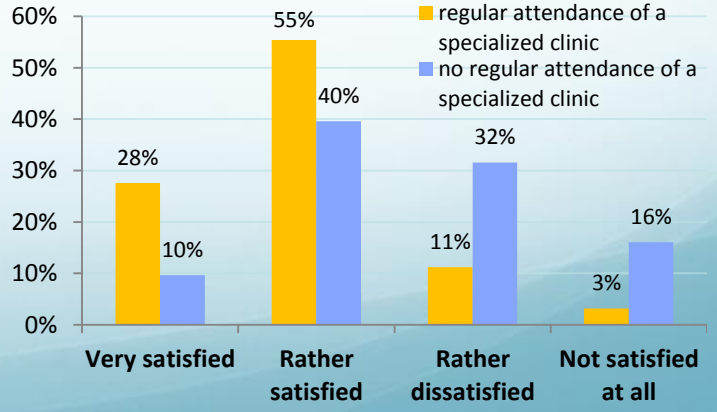


Current or past users of steroids



Patients who have **never** taken steroids

Overall satisfaction with medical treatment



Clinical trials in Duchenne muscular dystrophy

- *PTC124-GD-007:* Completed, recruitment 174 subjects
- *DMD117, DMD114 (PRO051):* Completed, recruited > 200
- *FOR DMD study:* active, recruiting (168 subjects already recruited, target: 225)

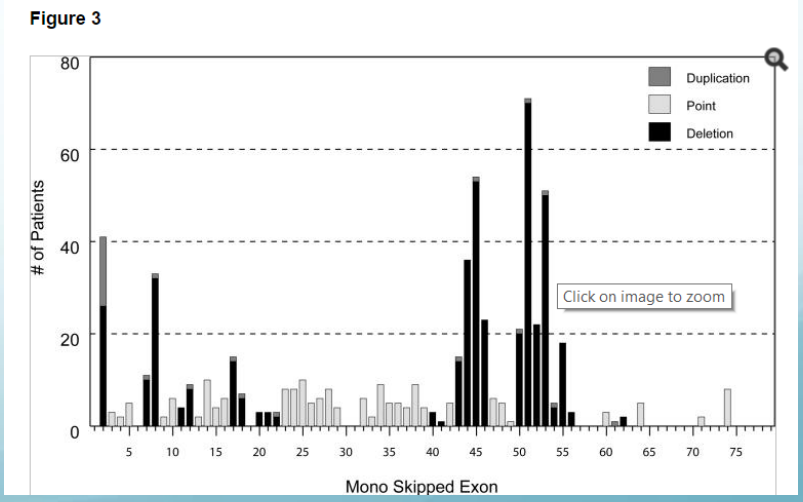
- Summit phase I-II
- Skip
- PRO045, PRO053
- Eli Lilly

- CAT-1004
- Epigallocatechin-Gallate
- ……..

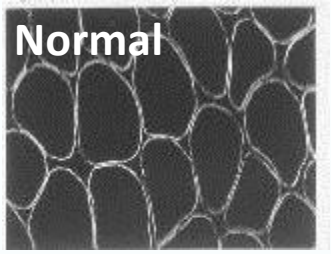
Exon skipping strategy in DMD

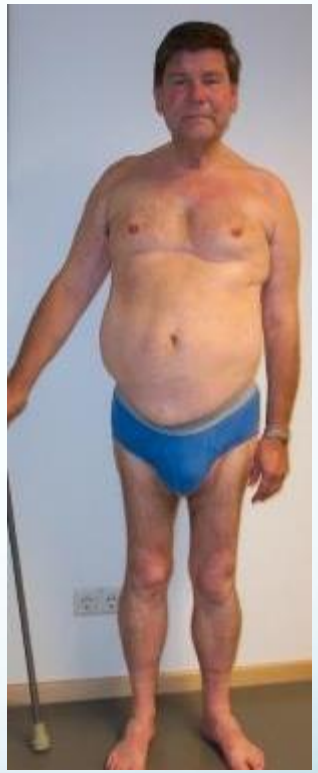
- Rare disease with limited eligible subjects
  - ~60% of DMD patients could benefit from exon skipping approach (Bladen CL et al, Hum Mutat 2015 Apr;36(4):395-402)
  - ~ 6% of DMD patients could benefit from single exon skipping drugs (Flanigan KM, et al., Hum Mutat. 2009 Dec;30(12):1657-66.

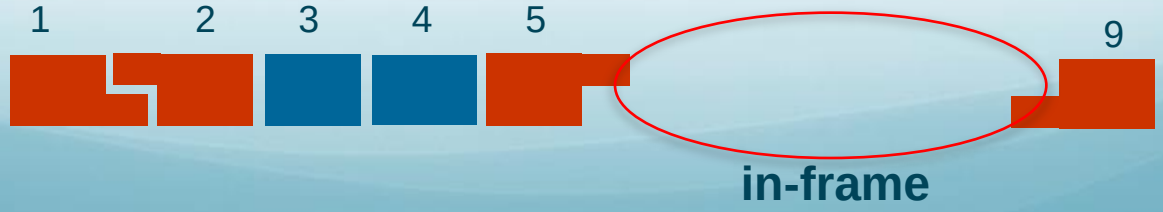
- Recruitment in exon skipping trials is therefore problematic

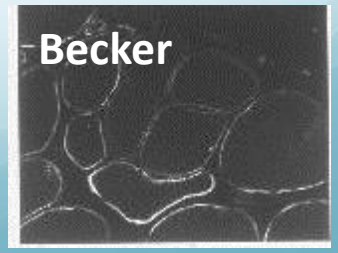


Exon skipping strategy in DMD



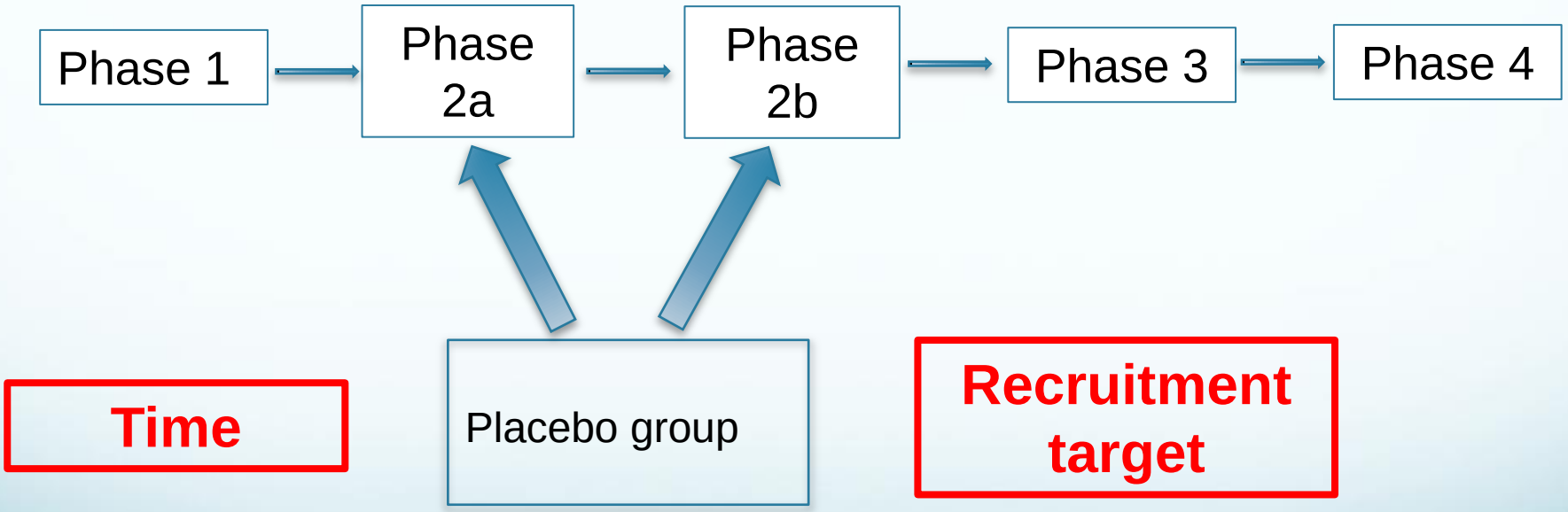






Exon skipping strategy in DMD

Drug development programme



Exon skipping strategy in DMD

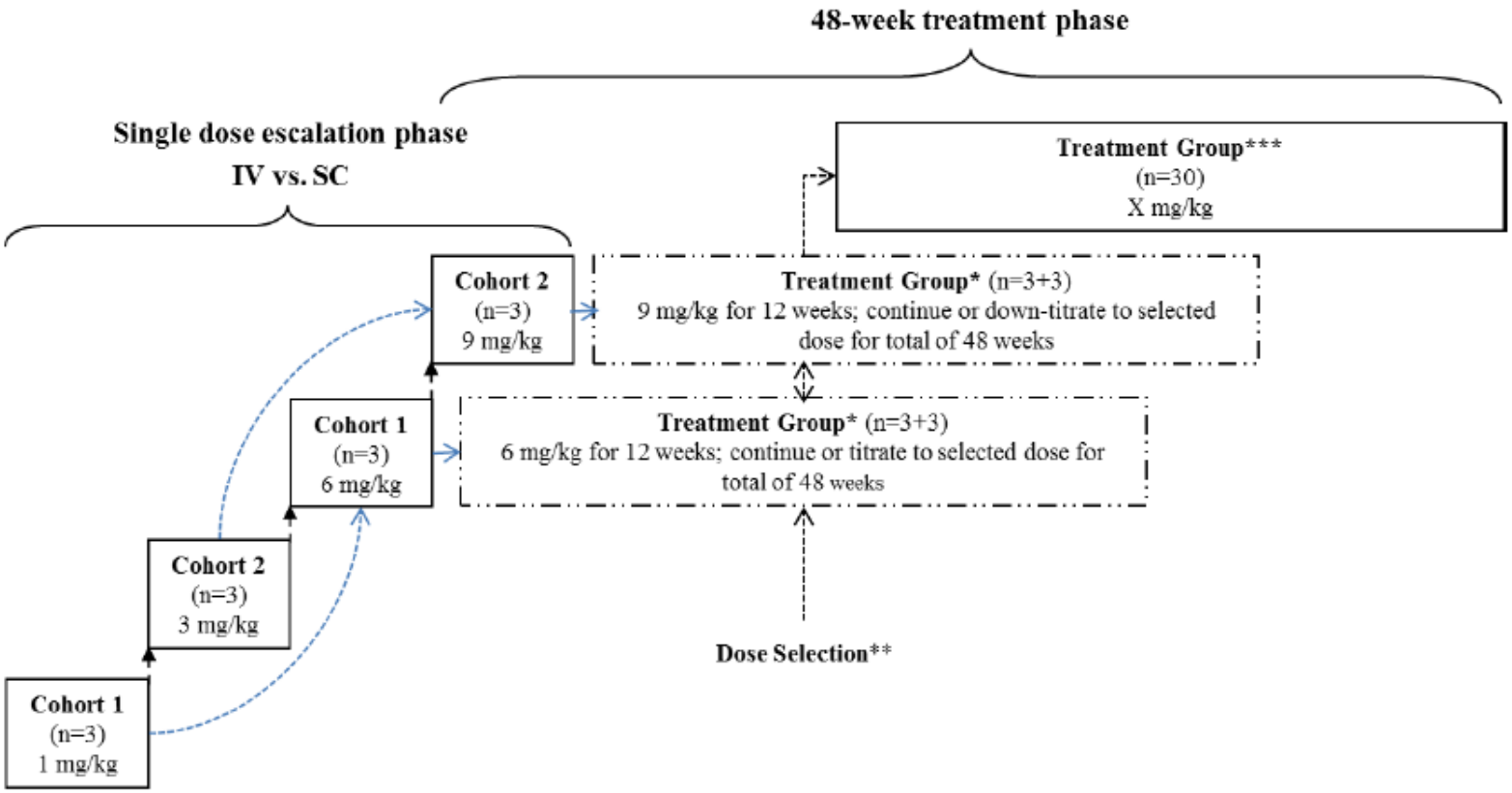
A Phase I/II, open-label, dose escalating with 48-week treatment study to assess the safety and tolerability, pharmacokinetics, pharmacodynamics and efficacy of exon skipping in subjects with Duchenne muscular dystrophy

- Primary objective:
  - To assess ***efficacy*** of study drug after 48 weeks of dosing in ambulant subjects with DMD
- Secondary objectives:
  - To assess safety and tolerability of study drug after ***single intravenous and subcutaneous*** dose
  - To investigate the ***pharmacokinetics*** and pharmacodynamics of study drug at different dosing regimes
  - To assess the safety and tolerability of study drug at different dosing regimes
- Number of subjects: 45

Exon skipping strategy in DMD

A Phase I/II, open-label, dose escalating with 48-week treatment study to assess the safety and tolerability, pharmacokinetics, pharmacodynamics and efficacy of exon skipping in subjects with Duchenne muscular dystrophy

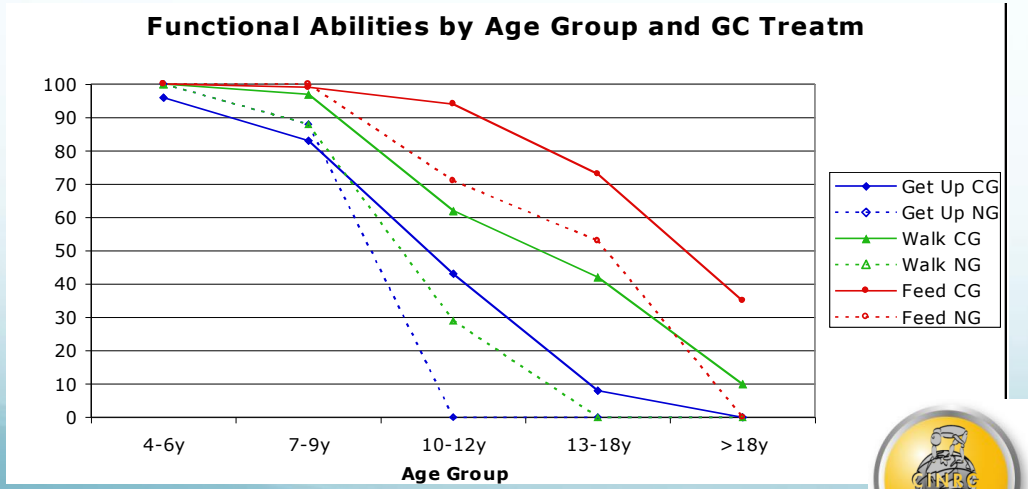
Figure 1 **Study design schematic**



Exon skipping strategy in DMD

Natural History data as placebo group

- Placebo-control data from other programmes
- Contemporaneous natural history data



C McDonald[1], and the CINRG Investigators[2-20]

Exon skipping strategy in DMD

Response from Ethics

Provisional opinion

The Committee noted that the filter sheet indicates this is a trial involving healthy volunteers. The application (A59) states that no controls are being recruited although the analysis (A62) does refer to control/natural history data.

You stated that currently there are three studies running internationally for the trial network and data will be gathered from these. There is no control data for the dose escalation phase however the aim is to try to match the baseline after 48 weeks in the treatment phase and control data will be compared. You clarified that control/natural history data is being collected outside the study (with appropriate consent in place) and this will be used to examine comparisons. Ms Morgan added that as this is a 'first in human' trial it is very important that there is comparability so you are examining comparisons over a 24 hour period to ensure consistency.

The Committee is unable to give an ethical opinion on the basis of the information and documentation received so far. Before confirming its opinion, the Committee requests that you provide the further information set out below.

Authority to consider your response and to confirm the Committee's final opinion has been delegated to the Chair/Vice Chair.

Further information or clarification required

1. The role, source and quantity of any control data should be clarified.

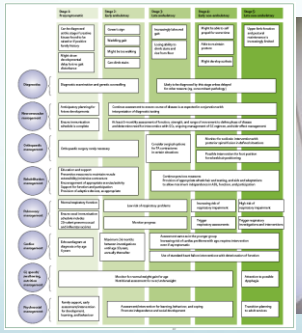
How to go around conducting a clinical trial in small populations: DMD

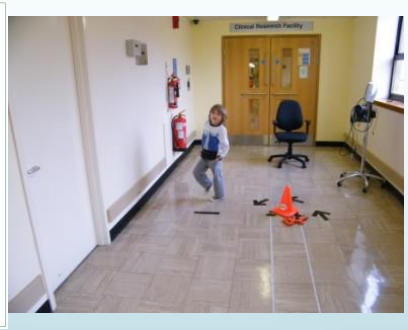
Patient registries

Standards of care and outcome measures

Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management

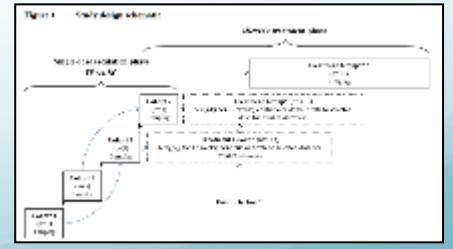
Katharine Bushby, Richard Finkel, David J Birnkrant, Laura E Case, Paula R Clemens, Linda Cripe, Ajay Kaul, Kathi Kinnett, Craig McDonald, Shree Pandya, James Poysky, Frederic Shapiro, Jean Tomezsko, Carolyn Constantin, for the DMD Care Considerations Working Group*





Natural history data

Trial site registry



Alternative study designs

TREAT-NMD Global Registries

NH data 1

NH data 2

NH data 3…

Legacy and ongoing natural history studies

TREAT-NMD Care and Trial Site Registry

Clinical user interface

Regulatory Compliant Disease Specific Postmarketing Protocols/Registries

STRIDE-NMD

Strategic Targeting of Registries and International Datasets of Excellence in Neuromuscular Disorders

THE John Walton MUSCULAR DYSTROPHY RESEARCH CENTRE

Thank You