

Research in Adult DMD

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Queen Square

What research is there?

- Medline search 'Duchenne muscular dystrophy'
 - 3751 publications
- 'AND Adult' (4216334 publications)
 - 657 publications (most not on adult DMD)
 - 22/100 'pure' adult DMD studies
 - Quality of life studies, carers burden, case series showing improved life expectancy (3/100)
 - biomarkers and outcome measures
 - Case reports (5/100)
- Clinical trials database (clinical trials.gov)
 - 167 studies
 - 14 include patients over 16 years

Name of study

Stem Cell Therapy in Duchenne Muscular Dystrophy

Research of Biomarkers in Duchenne Muscular Dystrophy Patients (IBISD)

Study Safety and Efficacy of BMMNC for the Patient With Duchenne Muscular Dystrophy

Open Label, Extension Study of PRO044 in Duchenne Muscular Dystrophy (DMD)

Eplerenone for Subclinical Cardiomyopathy in Duchenne Muscular Dystrophy (E-SCAR DMD)

Observational Study of Patients With Duchenne Muscular Dystrophy Theoretically Treatable With Exon 53 Skipping (pre U7-53)

Longitudinal Study of the Natural History of Duchenne Muscular Dystrophy (DMD)

Magnetic Resonance and Optical Imaging of Dystrophic and Damaged Muscle

Duchenne Muscular Dystrophy < 18y in Norway: Genotype/Phenotype, Growth, Puberty, Bone Health and Quality of Life

2D Strain Evaluation: Children With Duchenne Muscular Dystrophy Versus Healthy Children

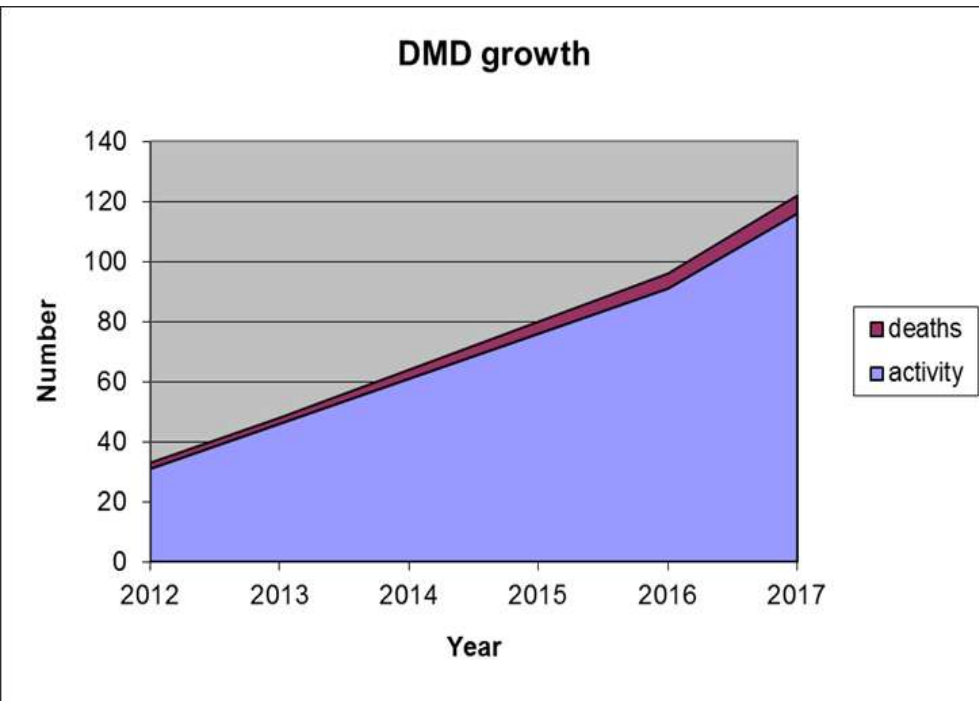
Clinical Intramuscular Gene Transfer Trial of rAAVrh74.MCK.Micro-Dystrophin to Patients With Duchenne Muscular Dystrophy

Therapeutic Potential for Aldosterone Inhibition in Duchenne Muscular Dystrophy

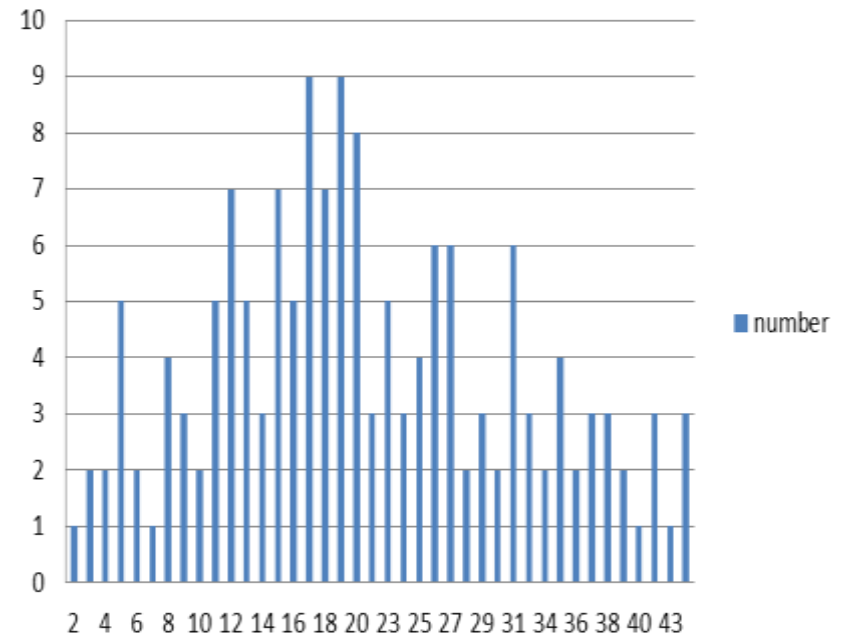
Testosterone Therapy for Pubertal Delay in Duchenne Muscular Dystrophy

Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of HT-100 in Duchenne Muscular Dystrophy

New and growing population of people with DMD



Queen Square



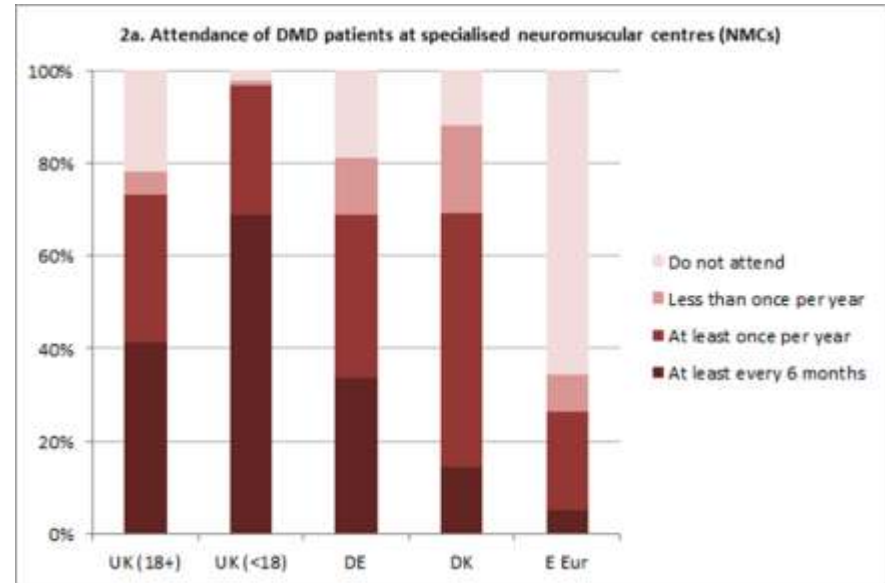
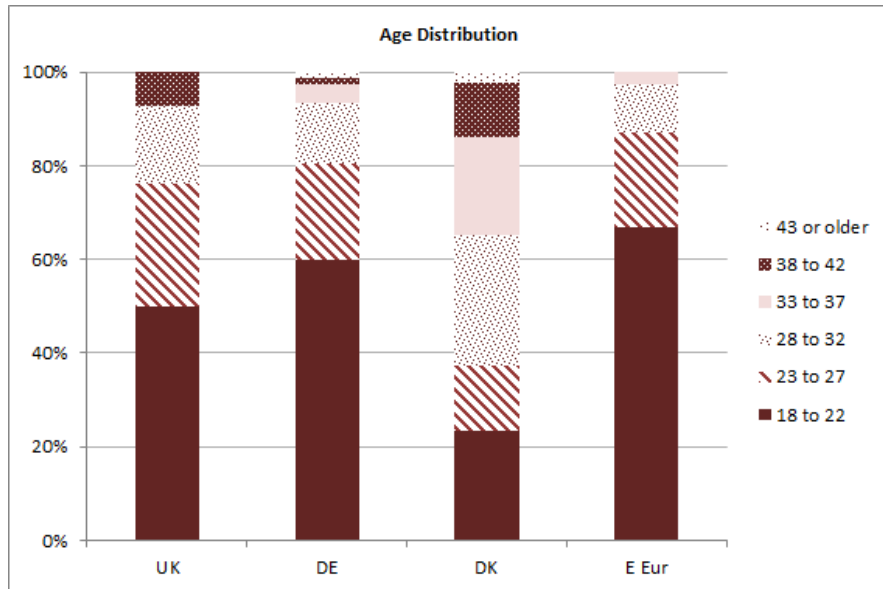
Denmark 2012 survival to 47 years
 Courtesy of Jes Rahbeck 2013



Care-NMD survey



Variable Outcome Across Europe



- UK more children than adults with DMD (83% < 27 years)
- Denmark 3x more adults than children, maximum age 47 years (44.2% < 27 years, over one third aged over 33 years)

- Courtesy of Dr Sunil Rodger Newcastle University (CARE NMD project)

J Neurol (2015) 262:629–641
DOI 10.1007/s00415-014-2385-3

ORIGINAL COMMUNICATION

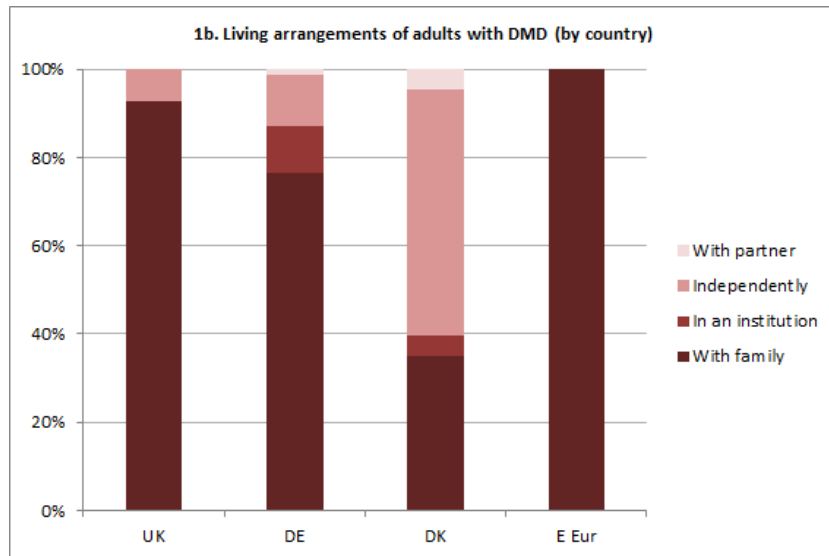
Adult care for Duchenne muscular dystrophy in the UK

Sunil Rodger · Katherine L. Woods · Catherine L. Blain · Angela Stringer · Julia Vry · Kathrin Grunsch · Justus Kirchler · Rachel Thompson · Katherine Roddy · Hans Lochmüller



Care-NMD survey

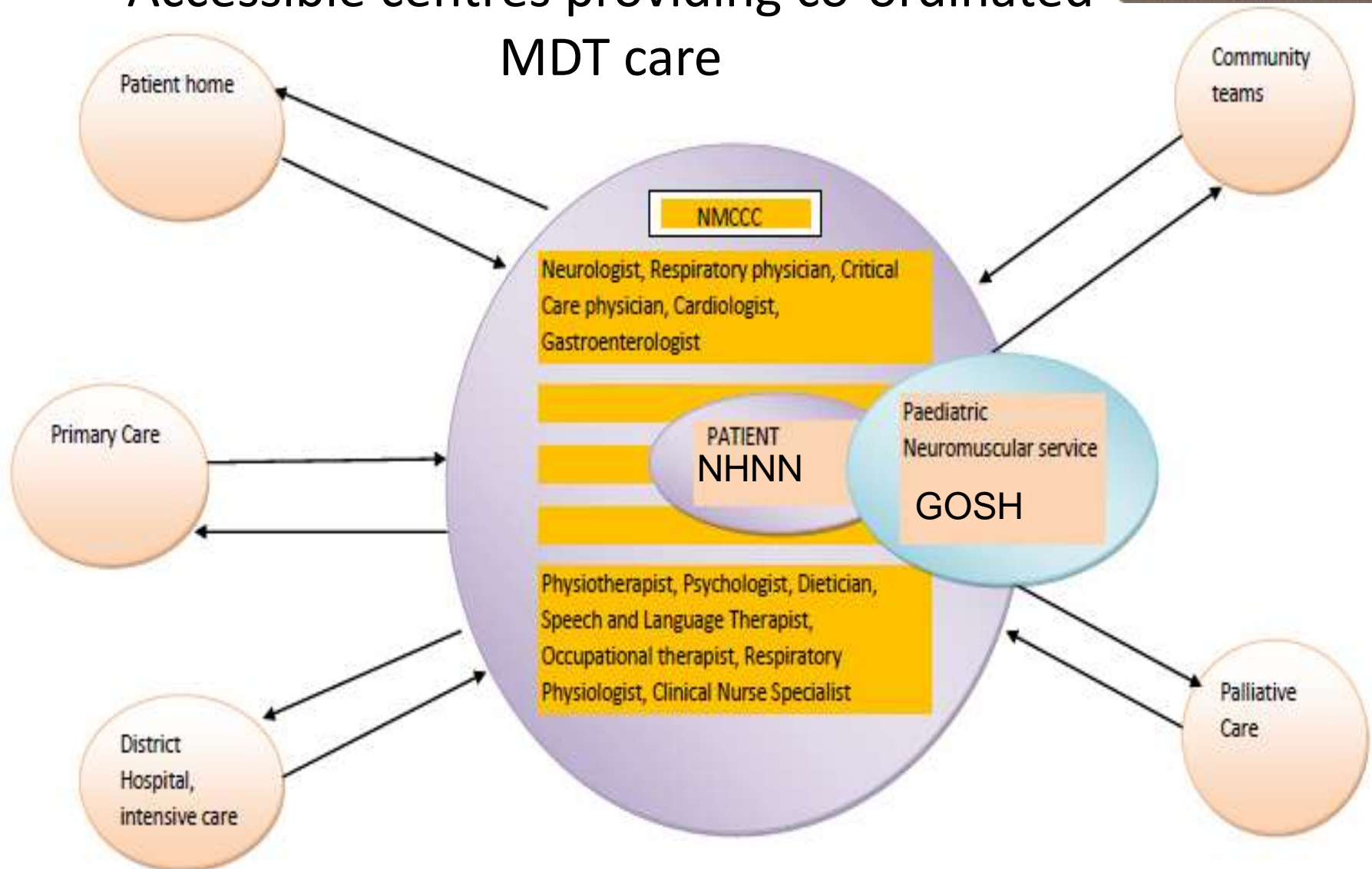
- Social inclusion in the UK much worse than other European countries
- Nearly 1/3 of adults not receiving recommended heart/lung checks
- Limited access to physiotherapy
- Adults are less likely to be satisfied with their care



‘Significant room for improving multidisciplinary care for this population in the UK’

Courtesy of Dr Sunil Rodger Newcastle University (CARE NMD project)

Accessible centres providing co-ordinated MDT care



Quinlivan, Matthews, Hanna:
Current Opinion in Neurology 2014

Develop a network of centres of
excellence for adults with DMD

North Star Network

- 17 participating centres
- 428/500 boys on data base had usable data
 - 396 steroid treated
 - 32 steroid naïve
 - 19 deflazacort
 - 15 alternate day
 - 154 10/10
 - 136 daily



RESEARCH PAPER

Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy

Valeria Ricotti,¹ Deborah A Ribout,² Elaine Scott,² Ros Quinivan,^{1,4} Stephanie A Robb,¹ Adnan Y Manzur,² Francesco Muntoni,^{1,4} on behalf of the NorthStar Clinical Network

JNNP 2012



Courtesy of Valeria Ricotti

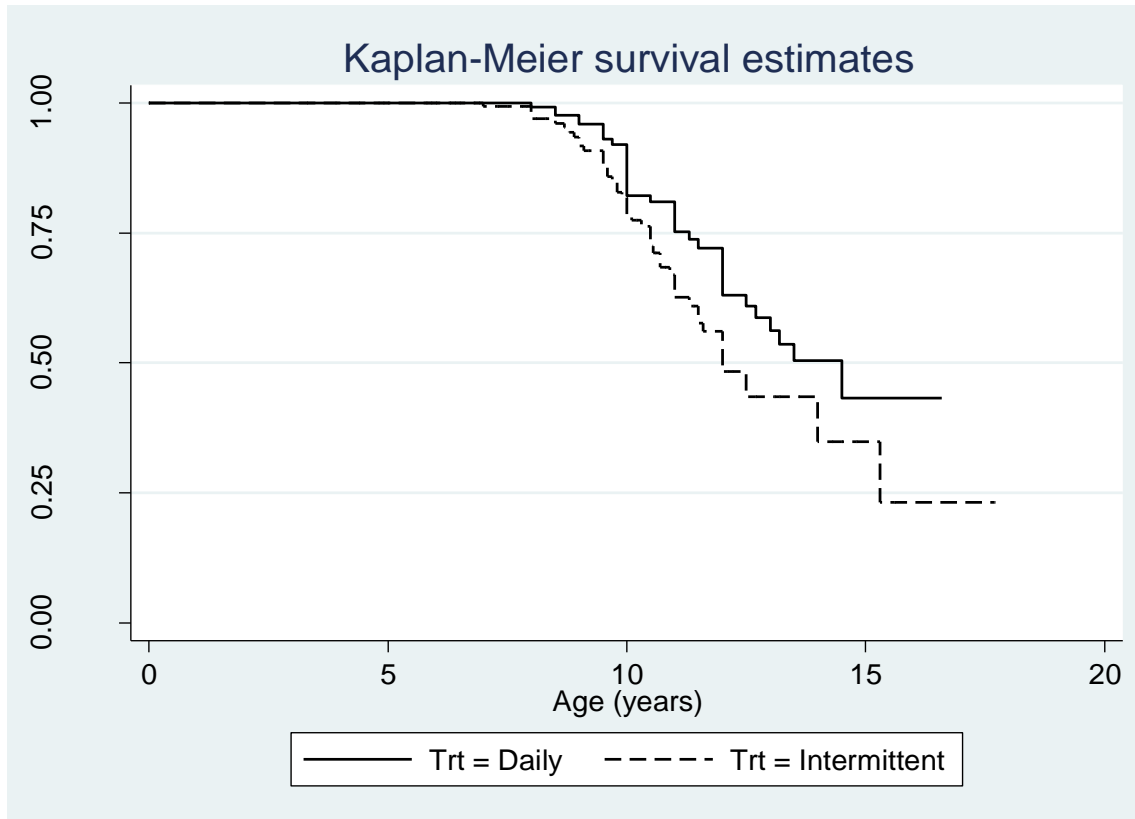
NorthStar Ambulatory Assessment

Box 1 The 17 items of the NorthStar Ambulatory Assessment

Stand
Walk
Stand up from chair
Stand on right leg
Stand on left leg
Climb box step—right leg
Climb box step—left leg
Descend box step—right leg
Descend box step—left leg
Gets to sitting
Rise from the floor
Lift head
Stand on heels
Jump
Hop—right leg
Hop—left leg
Run (10 m)



Age at Loss of Ambulation



- Loss of ambulation:
Intermittent 48/176
Daily 36/165
- Median age of LOA:
 - Intermittent = 12 years
 - Daily = 14.5 years

Courtesy of Valeria Ricotti

Courtesy of Valeria Ricotti

Table 3 Moderate to severe side effects breakdown, χ^2 analysis (intermittent prednisolone n=191; daily prednisolone n=169)

Side effects	Intermittent, n (%)	Daily, n (%)	χ^2 p value
Temper tantrums	54 (28)	67 (40)	0.02*
Mood swings	56 (29)	64 (38)	0.08
Aggressiveness	41 (21)	49 (29)	0.09
Hyperactivity	29 (15)	39 (23)	0.05*
Emotional lability	23 (12)	32 (19)	0.06
Insomnia	8 (4)	19 (11)	0.01*
Cushingoid features	28 (15)	56 (33)	<0.01*
GI symptoms	12 (6)	23 (14)	0.01*
Increased appetite	73 (38)	78 (46)	0.1
Hypertension	10 (5)	38 (22)	<0.01*
Vertebral fractures	8 (4)	14 (8)	0.1
Long bone fractures	13 (7)	9 (5)	0.5
BMD z-score $\leq -2.5^*$	9 (5)	14 (8)	0.1
Cataracts	2 (1)	4 (2)	0.3
Hirsutism	19 (10)	24 (14)	0.2
Easy bruising	5 (3)	7 (4)	0.4

*BMD z score=lumbar spine.

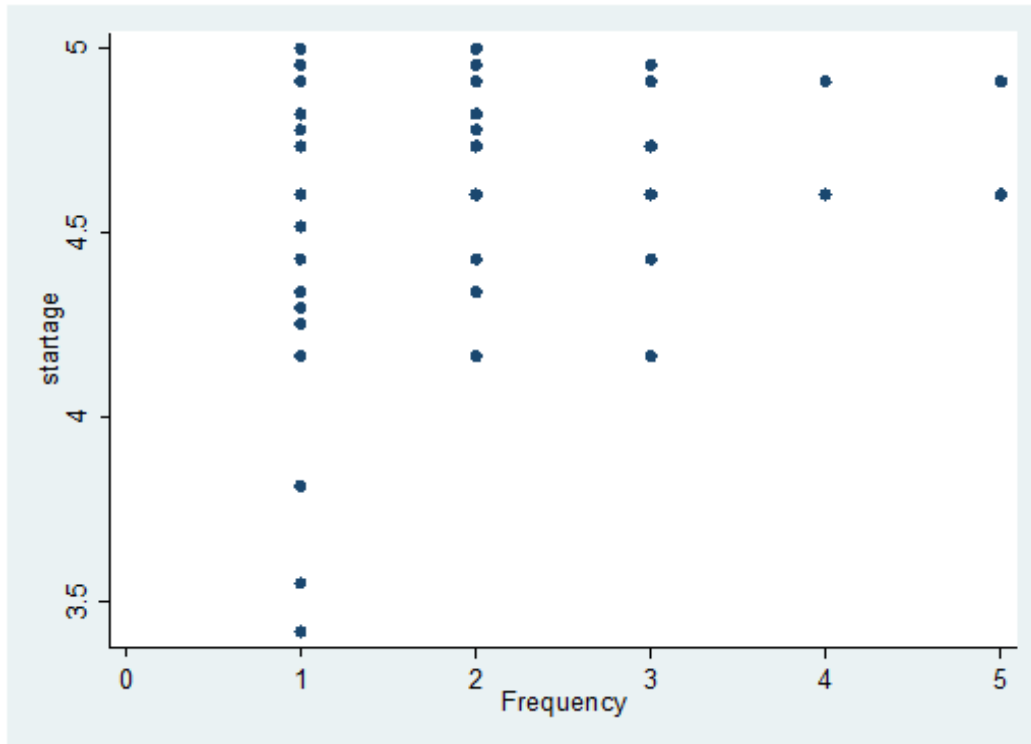
BMD, bone mineral density; GI, gastrointestinal.



Courtesy of Valeria Ricotti

DMD boys who started GC < 5 years of age

- **N = 36, mean age = 4.56 y (SD = 0.39)**
- The earliest starter = 3.42 years
- IP n= 17; DP n= 16; AD n= 3



**DMD boys
who started
treatment \geq 5
years**

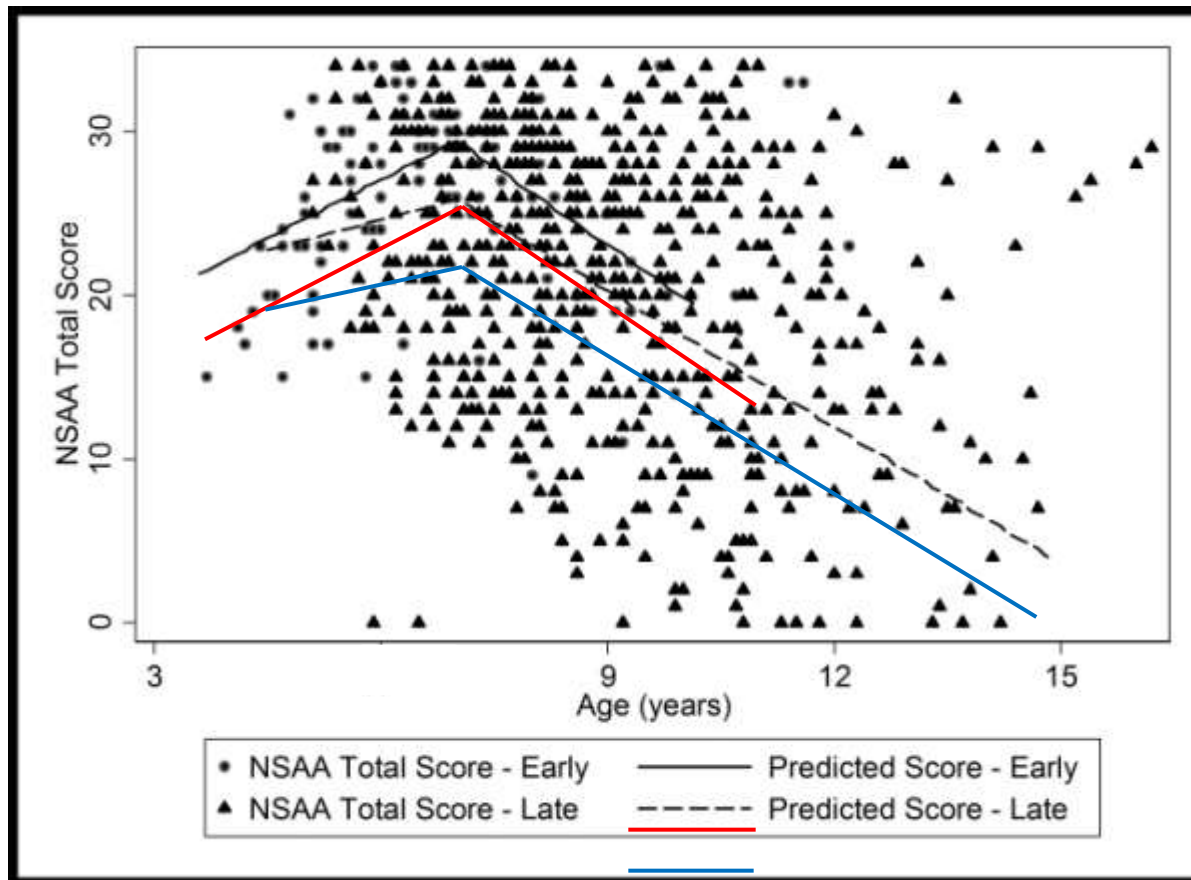
N= 222

**Mean = 6.83 y
(SD = 1.44)**



Courtesy of Valeria Ricotti

DMD boys who started GC < 5 years of age



- Before age 7 (n=36): early starters increase by an extra 2.04 units NSAA per year
- P=0.04



Courtesy of Valeria Ricotti

Adult 'North Star Network'

- Representatives from adult neurology centres met earlier this year at Queen Square
- A total of 650 adults with DMD were known to the group
- Need to develop centralised specialist Adult DMD services to co-ordinate care and develop research
- Standardised data collection
- Develop outcome measures

Important areas for research

- Transition (preparing people for adulthood)
- Natural history studies
- Outcome measures
- Quality of life and participation
- Physiotherapy/ hydrotherapy/ exercise
- Disease modifying therapies
 - Steroids, Exon skipping, Ataluren etc
- New technologies
 - Nano technology
 - Exo skeletons

OUTCOME MEASURES FOR NON AMBULANT DMD

Outcome measures: biomarkers

- Transcriptomics
- Proteomics
- Metabolomics

Proteomics Clin. Appl. 2014, 8, 269-278

DOI 10.1002/peca.201300072

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RESEARCH ARTICLE

Fibronectin is a serum biomarker for Duchenne muscular dystrophy

F. Cynthia Martin¹, Monika Hiller¹, Pietro Spitali¹, Sijm Oonk¹, Hans Dalebout², Magnus Palmblad², Amina Chaouch³, Michela Guglieri³, Volker Straub³, Hanns Lochmüller³, Erik H. Niks⁴, Jan J. G. M. Verschuuren⁴, Annemieke Aartsma-Rus^{1,3}, André M. Deelder², Yuri E. M. van der Burg² and Peter A. C. 't Hoen¹

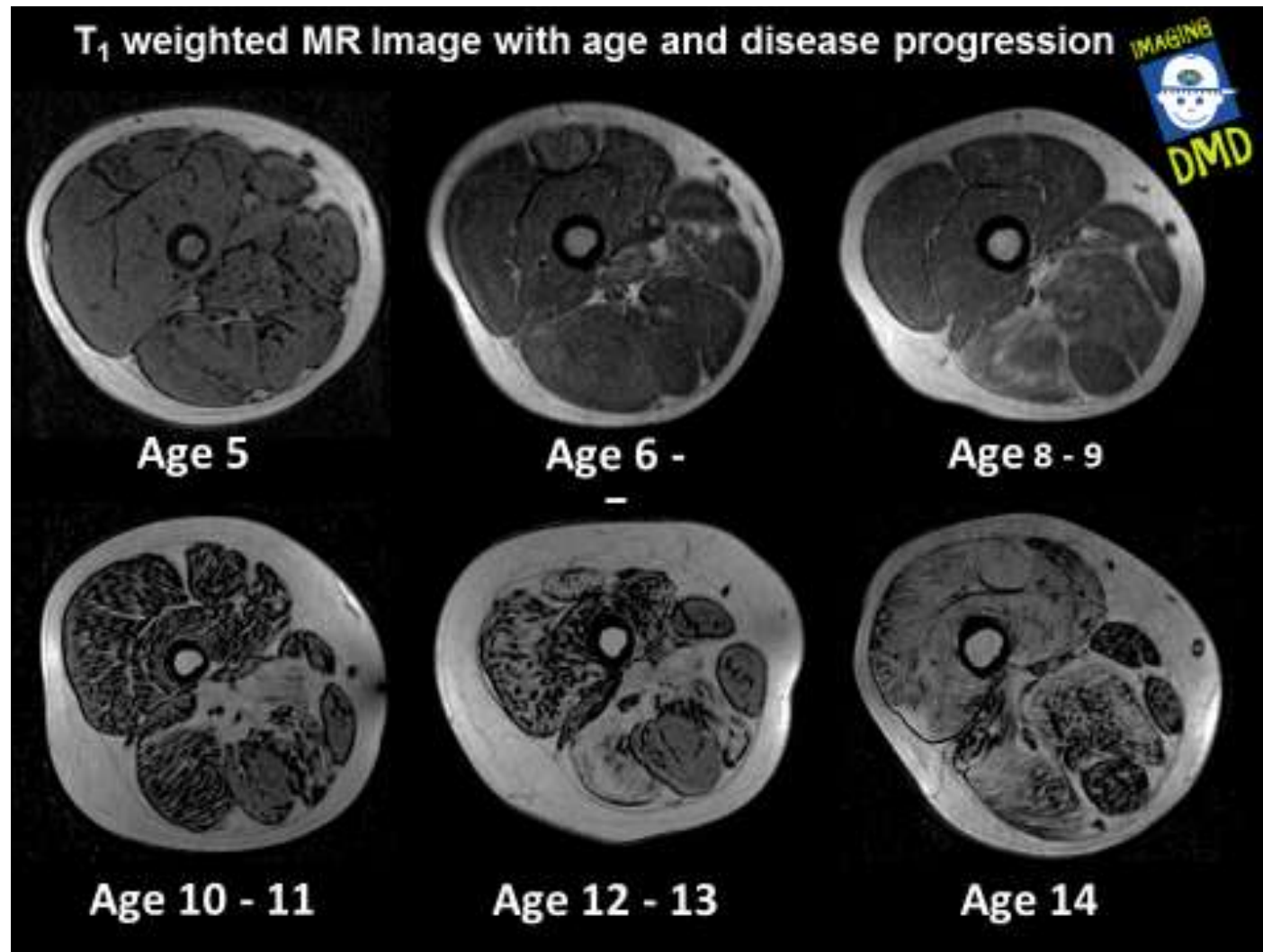
¹ Department of Human Genetics, Leiden University Medical Center (LUMC), RC, Leiden, The Netherlands

² Center for Proteomics and Metabolomics, Leiden University Medical Center (LUMC), RC, Leiden, The Netherlands

³ Institute of Genetic Medicine, Newcastle University, International Centre for Life, Newcastle upon Tyne, UK

⁴ Department of Neurology, Leiden University Medical Center (LUMC), RC, Leiden, The Netherlands

MRI Imaging



Lee Sweeney: courtesy of PTC bio

Six minute walk test most validated clinical endpoint utilized in ambulatory DMD trials

2008 ataluren '007	2010 drisapersen	2013 tadalafil	2013 ACT DMD	2015 eteplirsen	2015 Anti-myostatin
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**Primary
Endpoint**

6MWD

Stair Climb

**Secondary
Endpoints**

Time to 10% 6MWD Worsening

10-meter walk/run

Stair climb

Stair descend

North Star Ambulatory Assessment

PedsQL

PODCI

Myometry

Note: ataluren study conducted by PTC Therapeutics; drisapersen study conducted by GSK / Prosensa (Biomarin); tadalafil study conducted by Lilly; eteplirsen study conducted by Sarepta; anti-myostatin mAb study conducted by Pfizer.

Outcome measures: Clinically meaningful

- Respiratory Function
- EK scale
- Upper limb function
- Cardiac function



Outcome reliability in non-ambulatory boys/men with Duchenne muscular dystrophy.

Connolly AM; Malkus EC; Mendell JR; Flanigan KM et al

Muscle and Nerve 51(4):
522-32, 2015

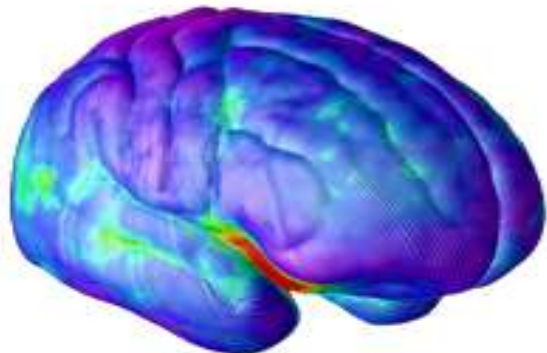
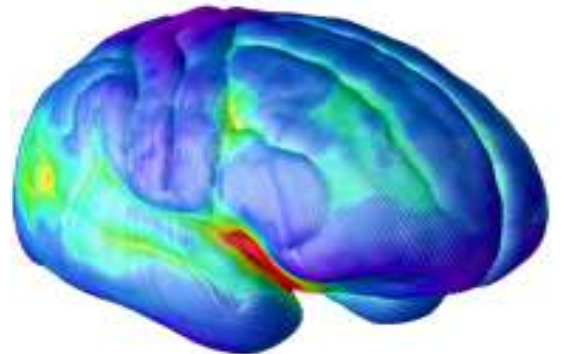
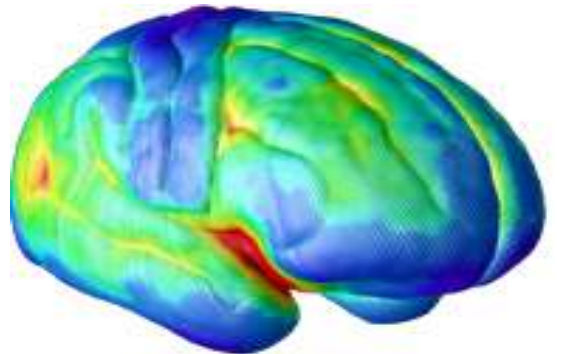
TRANSITION: PREPARING PEOPLE FOR ADULTHOOD

Health care behaviours in young adults with chronic disease

- Failure to engage with services/ non-attendance/
poor compliance
- Diabetes HbA1c worse
- Cancer outcomes improving slowest
- 50% of all psychiatric diagnoses
emerge by 14 years and 75% by 24 years
- 1:10 18 year olds have depression



Cognitive development



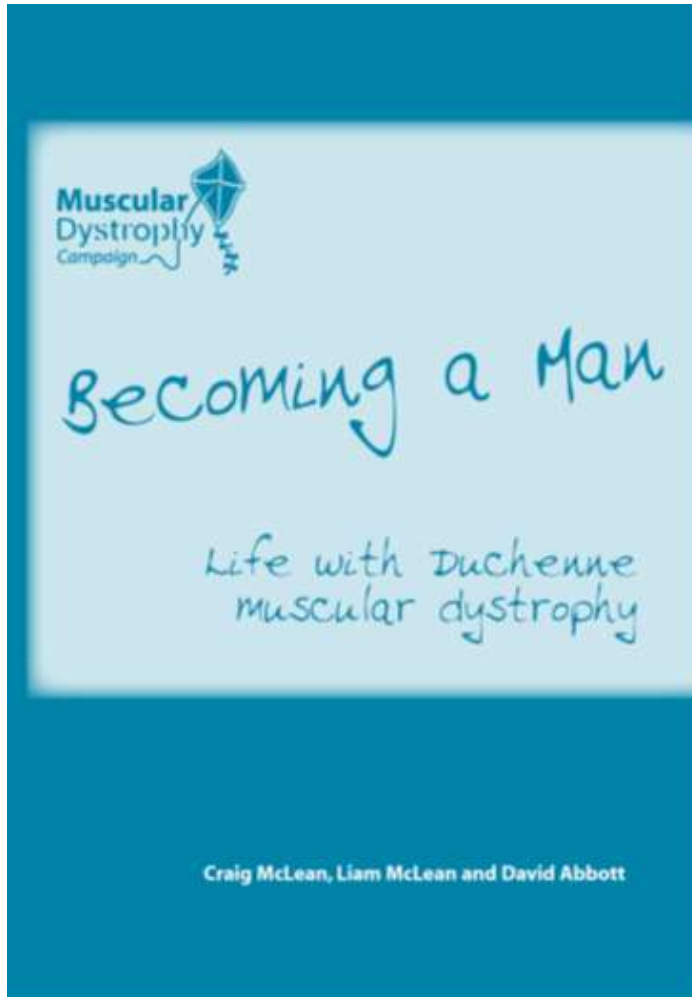
- Prefrontal cortex maturation
 - impulse control
 - planning
 - emotional regulation
- Limbic system hypersensitive
 - Continues into 3rd decade

Transition to adulthood: Road Map for Adolescent Growth

Carl Pickhardt 2009

- Four stages
 - Stage 1 (9-13 years)
 - Letting childhood go
 - Stage 2 (13-15 years)
 - Forming a family of friends
 - Stage 3 (15-18 years)
 - Acting more grown up
 - Stage 4 (18-22 years)
 - Stepping off on one's own





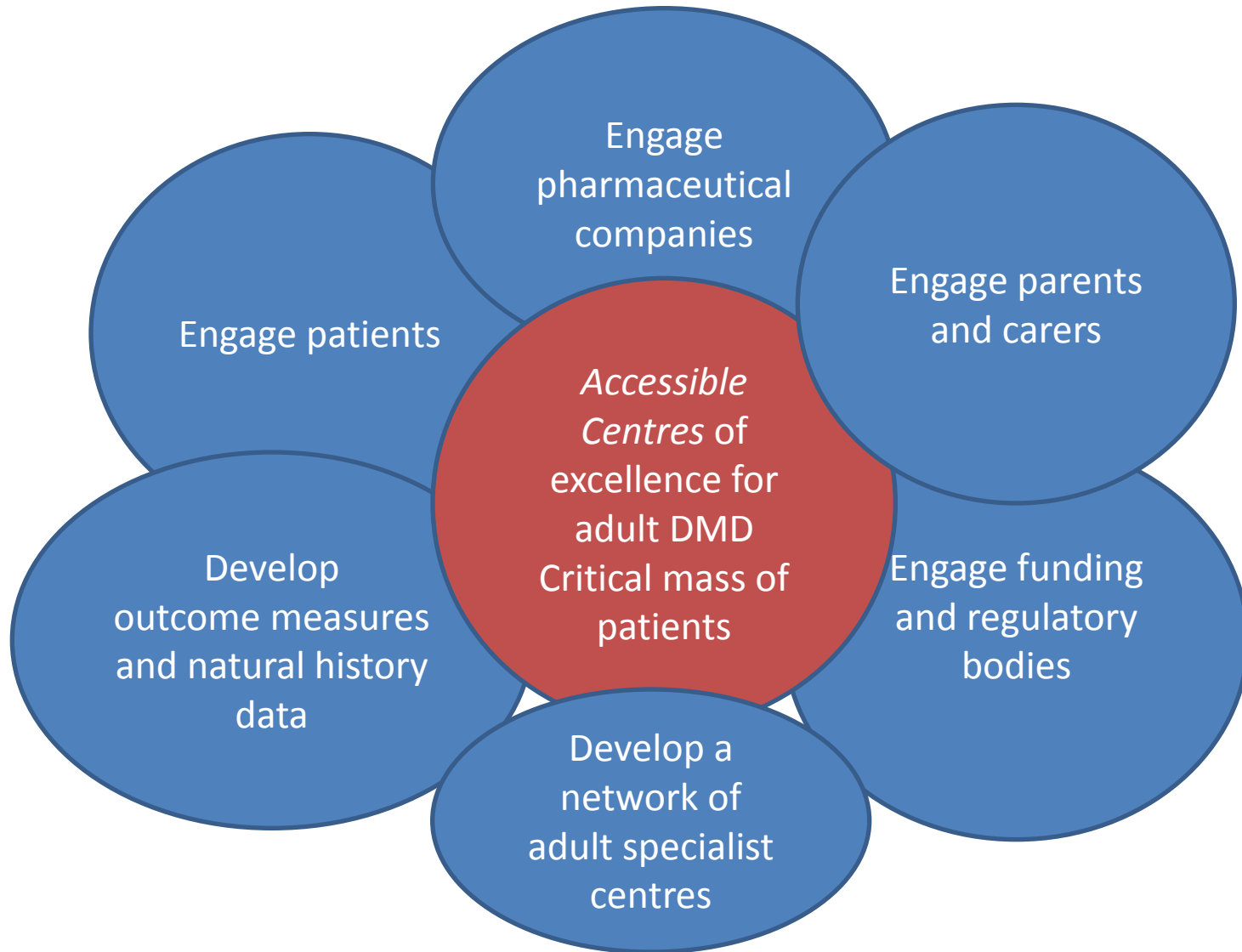
**TAKIN
CHARGE!**



New Technologies



What needs to change to develop adult DMD research in the UK?



Summary

- Rapidly growing new population of adults with DMD
- There is an urgent need to develop centres of excellence co-ordinating multi-disciplinary care and build a 'critical mass' of patients
- Research needs to focus on natural history, quality of life, participation and outcome measures before therapeutic trials can be designed
- We need to engage funding and regulatory bodies