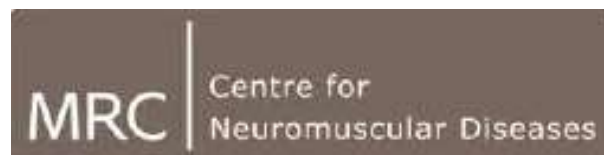


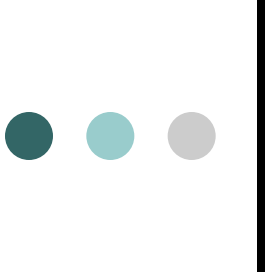
# Improving trial design and outcome measures for DMD

Kate Bushby

TREAT-NMD network co-ordinator

University of Newcastle, UK





# What trials should we do and how should we do them?

- How do we understand the animal studies to pick the best candidates?
- How do we understand the best way to study the drugs in patients?
  - To give us the best chance of successful therapies
- Key to this: TRIAL DESIGN AND OUTCOMES (in mice and men.....)

# Genes to therapies

Gene identification



Therapy delivery

## Dystrophin

Sarcoglycans

Dysferlin

Calpain 3

Lamin A/C

FKRP

Laminin alpha 2

Collagen VI

TRIM32

POMT1

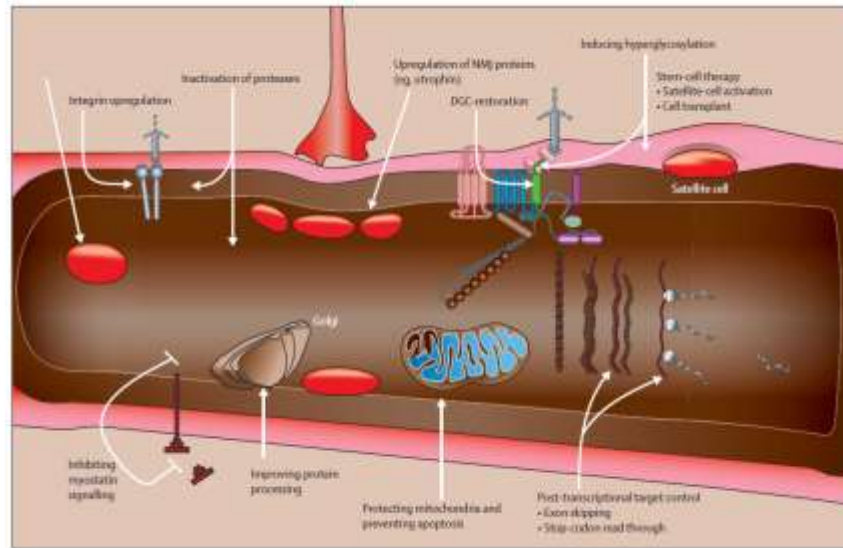
SEPN1

ANO5

LARGE

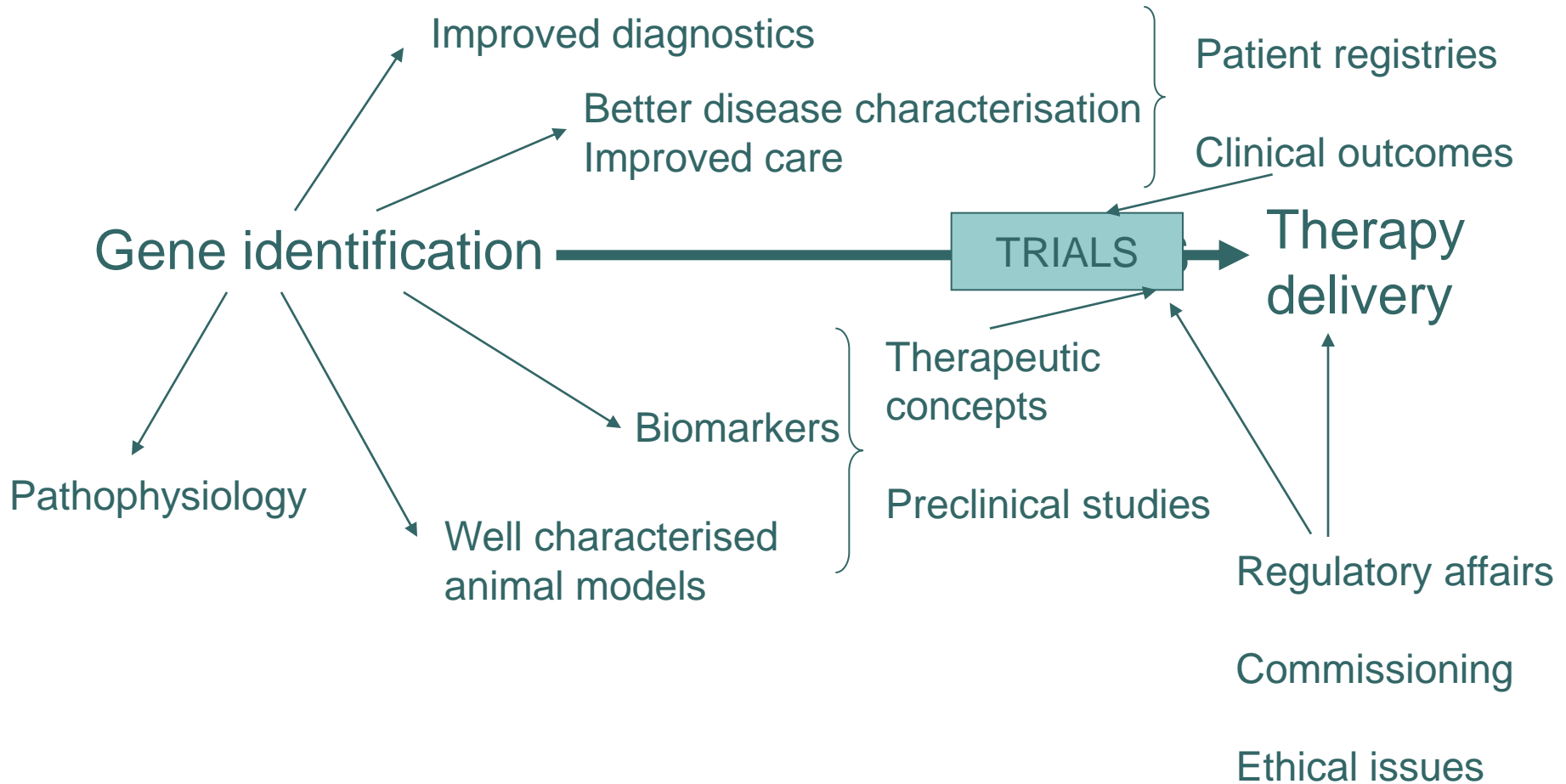
Myotilin

Titin.....

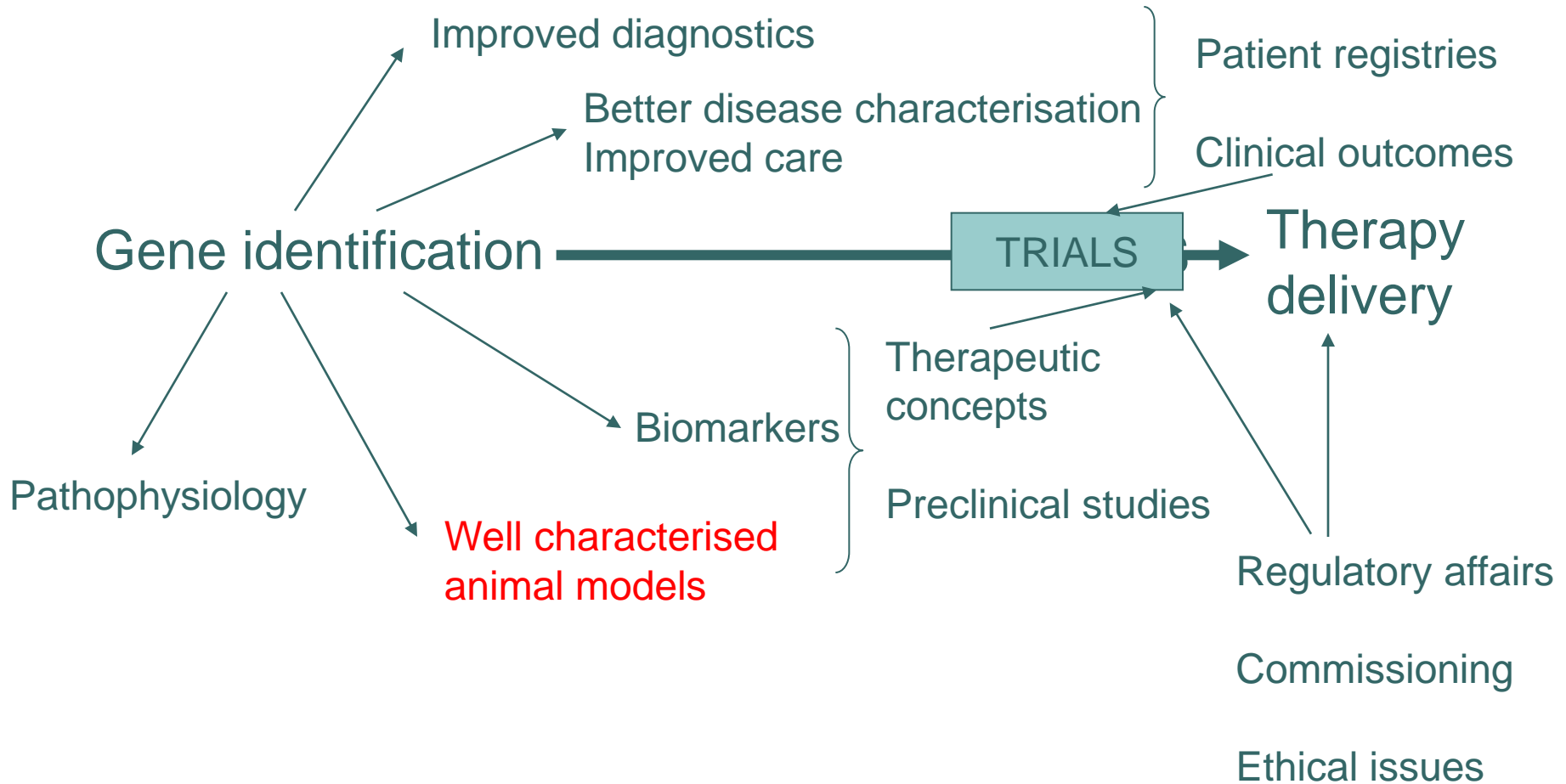


Bushby et al, Lancet 2009

# From gene identification to therapy delivery



# From gene identification to therapy delivery



# Mice to men

- Learning from DMD and other diseases (MND, ALS, Alzheimers)
- What model?
- How to test it?
- Which papers to believe?



## Preclinical Research

RESEARCH > PRECLINICAL RESEARCH > EXPERIMENTAL PROTOCOLS

### PRECLINICAL RESEARCH

Preclinical Research  
Animal Models

» Experimental Protocols

### OUTCOME MEASURES

REGULATORY ADVISORY  
SUPPORT

BIOBANKS

JOB OPPORTUNITIES

## Experimental Protocols

The availability of standardized operating procedures (SOPs) to unify experimental protocols used to test the effects of new treatments in animal models is a step that will undoubtedly improve the comparability of studies from different laboratories.

One of the goals of TREAT-NMD is to create a collection of SOPs that can be used as guidelines in the conduct of preclinical studies on mice and dogs. In full collaboration with the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center at Children's National Medical Center in Washington DC ([www.wellstone-dc.org/dod/ProjectsandCores/Murinedrugscreeningandtransgeniccore/tabid/288/Default.aspx](http://www.wellstone-dc.org/dod/ProjectsandCores/Murinedrugscreeningandtransgeniccore/tabid/288/Default.aspx)) and with the US National Institutes of Health (NIH)-Wellstone Muscular Dystrophy Cooperative Network ([www.wellstonemdcenters.nih.gov](http://www.wellstonemdcenters.nih.gov)), two meetings were hosted with specialists from all over the world to create a set of SOPs for a number of experimental protocols in the mdx mouse and GRMD dog models. These workshops were generously supported by Foundation to Eradicate Duchenne Inc ([www.duchennemd.org](http://www.duchennemd.org)), the US National Institutes of Health ([www.wellstonemdcenters.nih.gov](http://www.wellstonemdcenters.nih.gov)) and TREAT-NMD. These workshops were described in a meeting report published in *Neuromuscular Disorders* and available [here](#).

These SOPs are not meant to be mandatory but are designed to be a point of reference and should not prevent innovation and further improvement of the existing protocols.

The SOPs that have already been completed can be downloaded from this site and others will be added in the future. To ensure reproducibility and quality, each SOP has been drawn up by a group of independent researchers (listed as authors in each protocol) and will be updated on a regular basis.

If you wish to assist us by providing us with feedback about the content of these



### Downloads

Behavioral and locomotor measurements using open field animal activity monitoring system

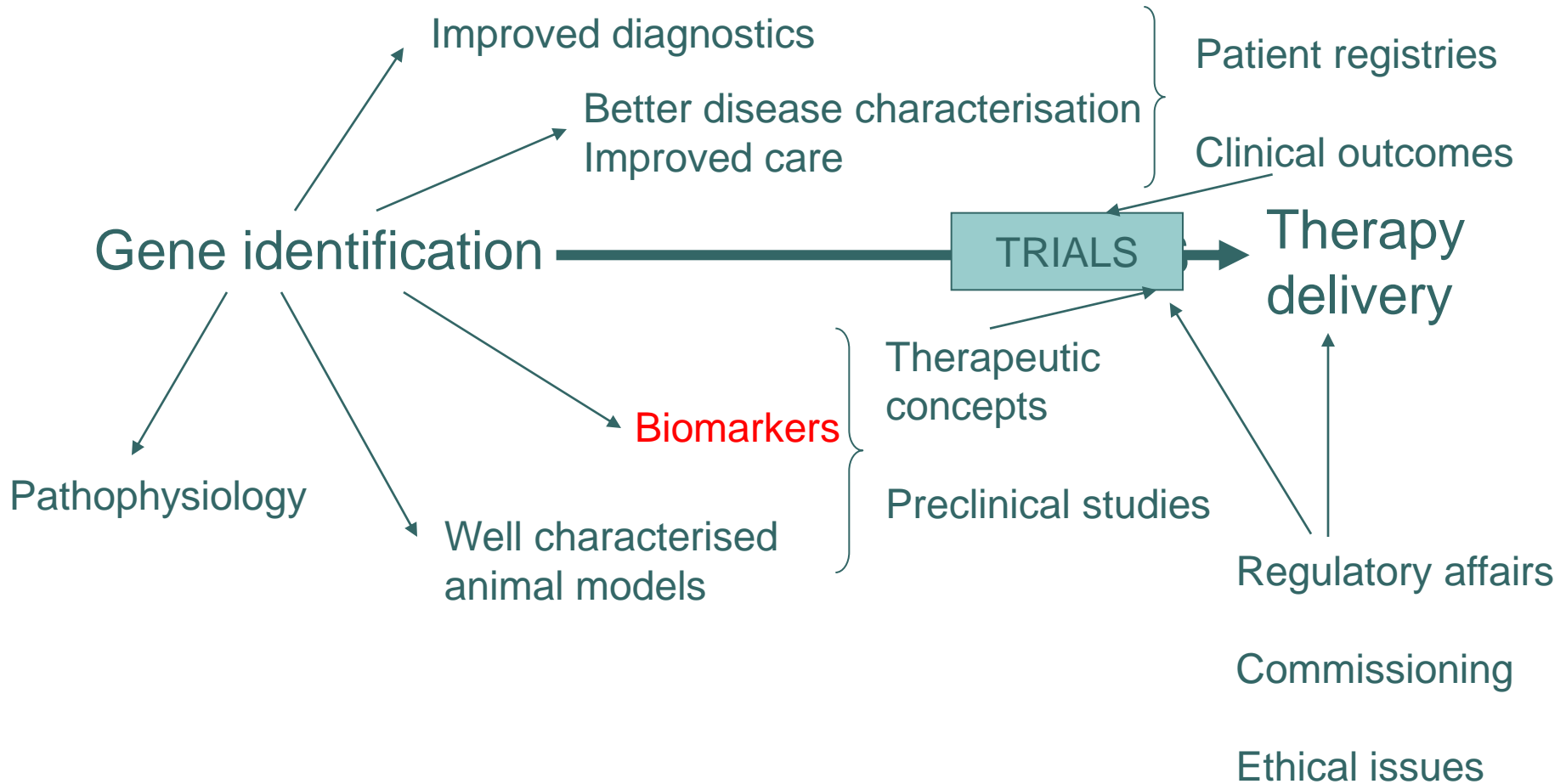
Whole body tension measurements

The recovery score to evaluate therapy efficacy in NMD: a common, quantitative and comparative scoring system

Use of treadmill and wheel exercise for impact on mdx mice phenotype



# From gene identification to therapy delivery

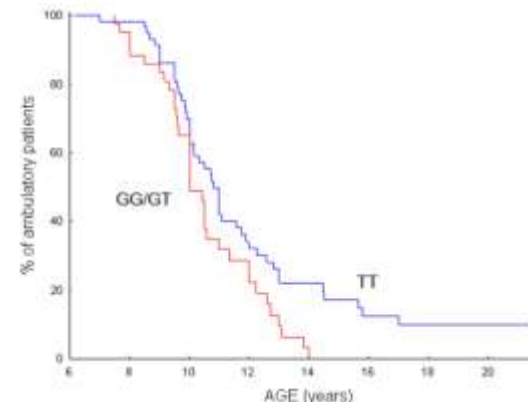


# Biomarkers

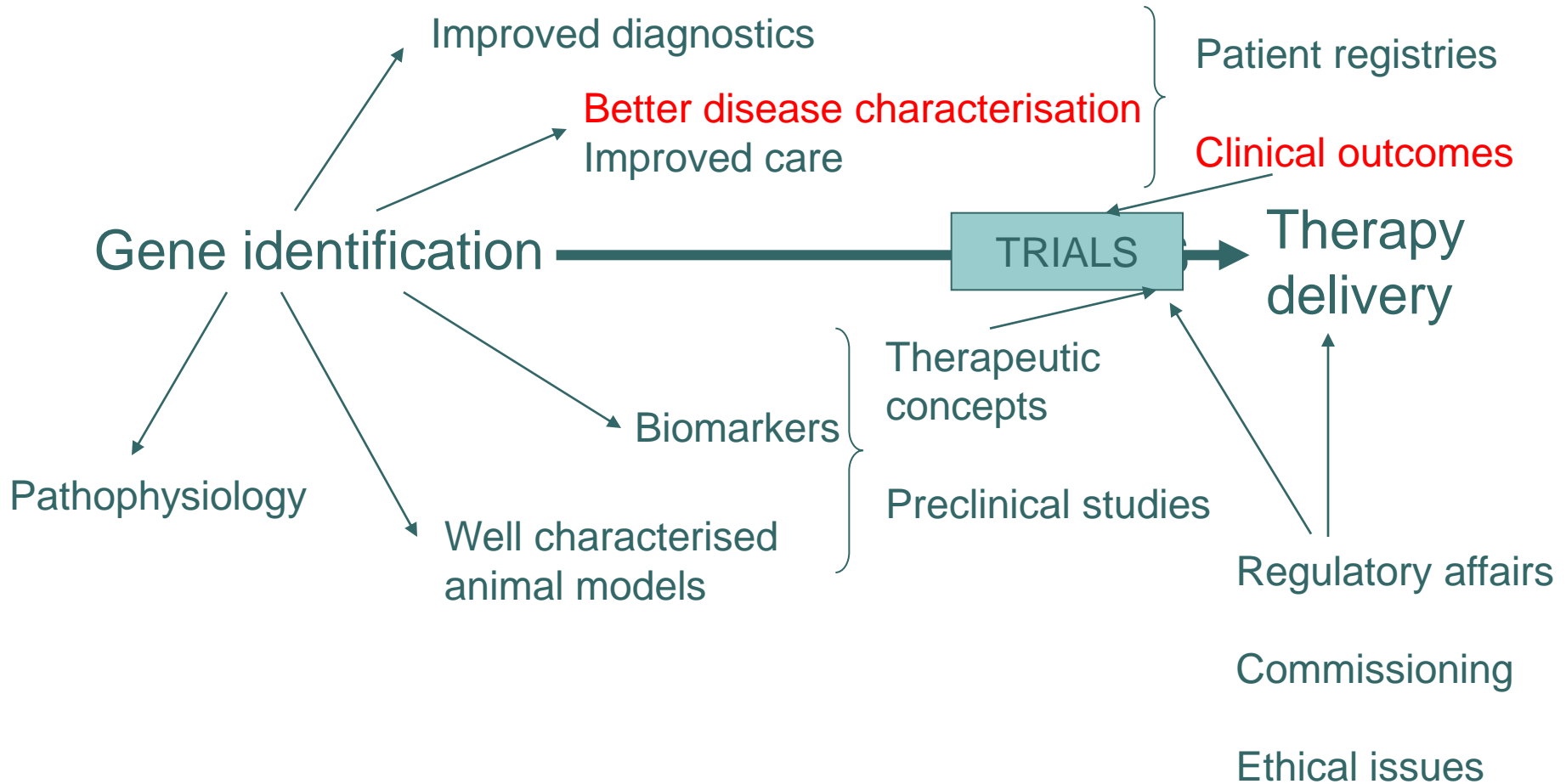
- Biomarkers to determine stratify disease severity or drug response
- Require high throughput methodologies and stringent verification
- Possible means to improve trial design and predict drug response
- No biomarkers are yet qualified in DMD

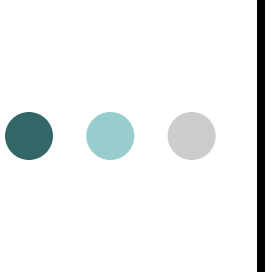


Dr Alessandra Ferlini



# From gene identification to therapy delivery





# How do we measure “outcomes”?

- No “one size fits all”
  - Depends on trial design and phase, patient group under study
- Different domains to be captured (see TREAT-NMD ROM)
  - Clinically meaningful change is key (regulatory definition)
  - Function
  - Strength
  - Patient reported outcomes
  - Biomarkers, others
- Primary and secondary outcomes need to be defined upfront



# Examples of different outcomes that have been used in DMD

- Strength (manual testing or using machines)
  - Functional scales (HAMA, North Star)
  - Timed tests (walk, stair climb, up from floor)
  - Six minute walk test
  - QOL
  - Dystrophin data
- 
- How do these outcomes relate to the clinical experience of the patient and family?

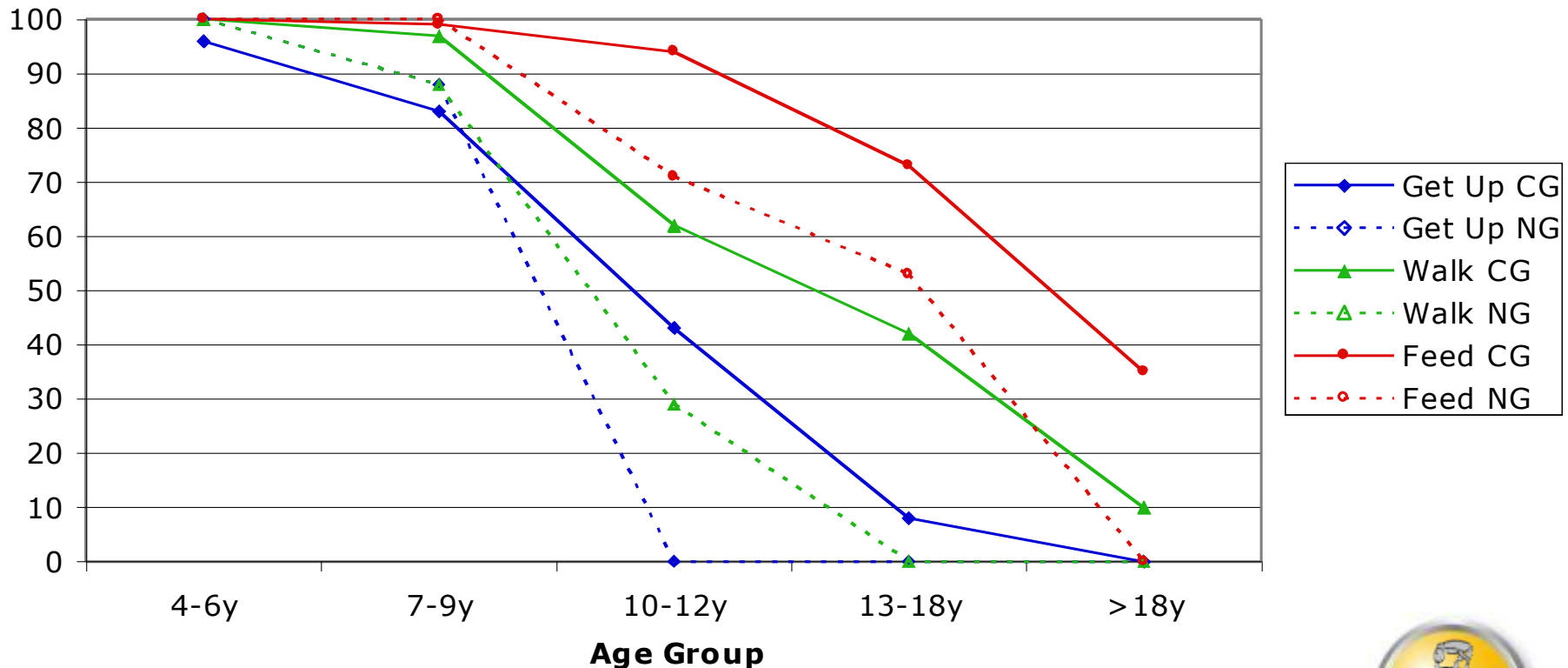
# “The new” natural history (DMD)

- Meeting in Washington DC June 2010
- Data from >1500 boys with DMD in natural history studies shared
- Consistent data on natural history
- Relationship of core measures to clinical endpoints clarified



# Relationship between measures and endpoints

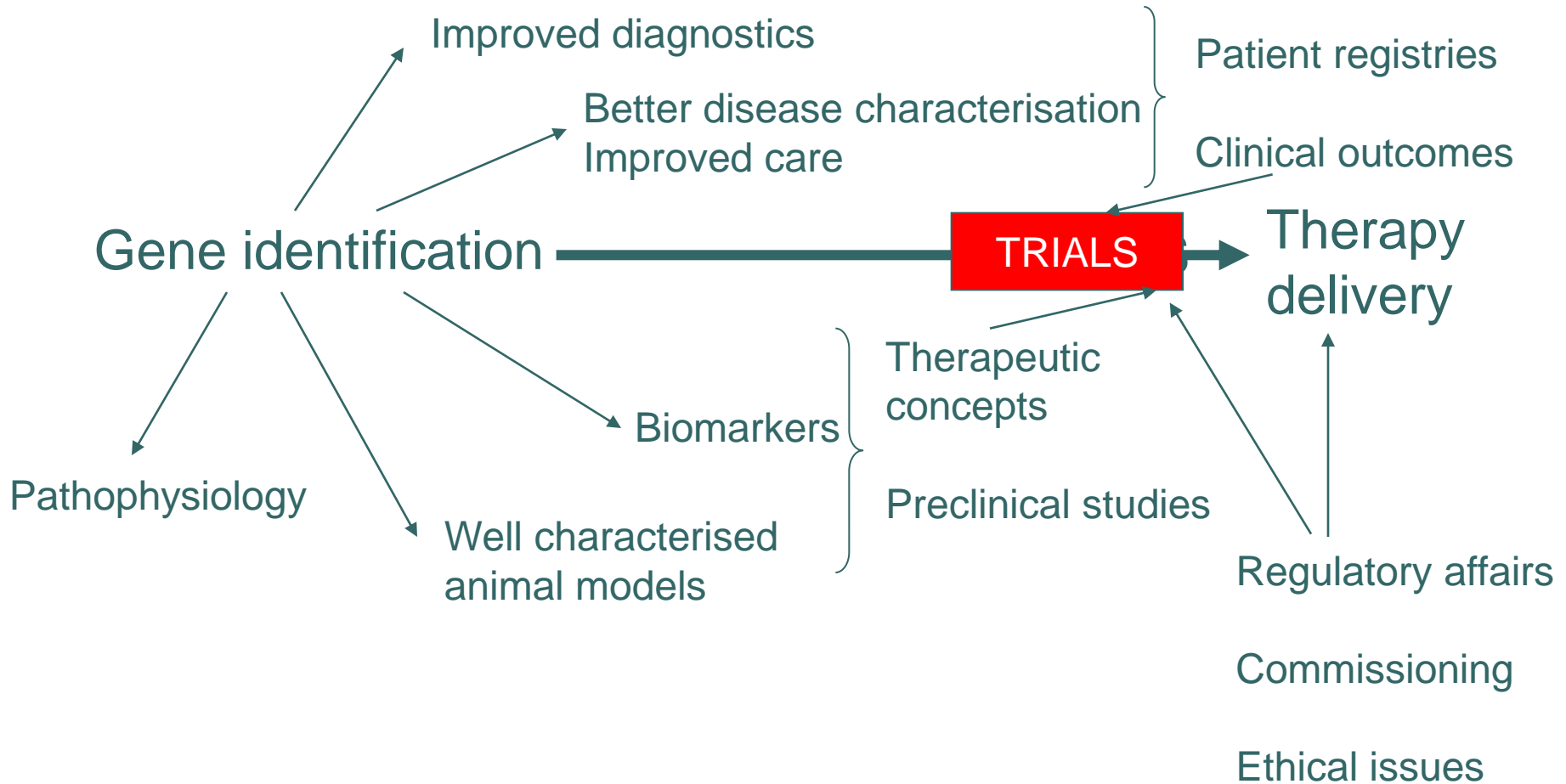
## Functional Abilities by Age Group and GC Treatm



C McDonald<sup>1</sup>, RT Abresch<sup>1</sup>, E Henricson, J Han<sup>1</sup>, R Leshner<sup>6</sup>, E Hoffman<sup>6</sup>, D Escolar<sup>6</sup>, A Cnaan<sup>6</sup>, F Hu<sup>6</sup>, A Zimmerman<sup>6</sup>, T Duong<sup>6</sup>, J Mayhew<sup>14</sup>, J Florence<sup>13</sup>, A Arrietta<sup>6</sup> and the CINRG Investigators<sup>2-20</sup>



# From gene identification to therapy delivery



# TACT - TREAT-NMD Advisory Committee for Therapeutics



- The pathway from a promising idea to drug registration is complex and requires multiple areas of expertise
- Very few individual groups have experience over the whole process of drug development, clinical trial design and regulatory implications
- Easy mistakes can be avoided with good advice
  - Based on a multidisciplinary and pragmatic approach to the problem

# The application and appraisal process

- The application form is available on the TREAT-NMD website and interested groups should submit applications



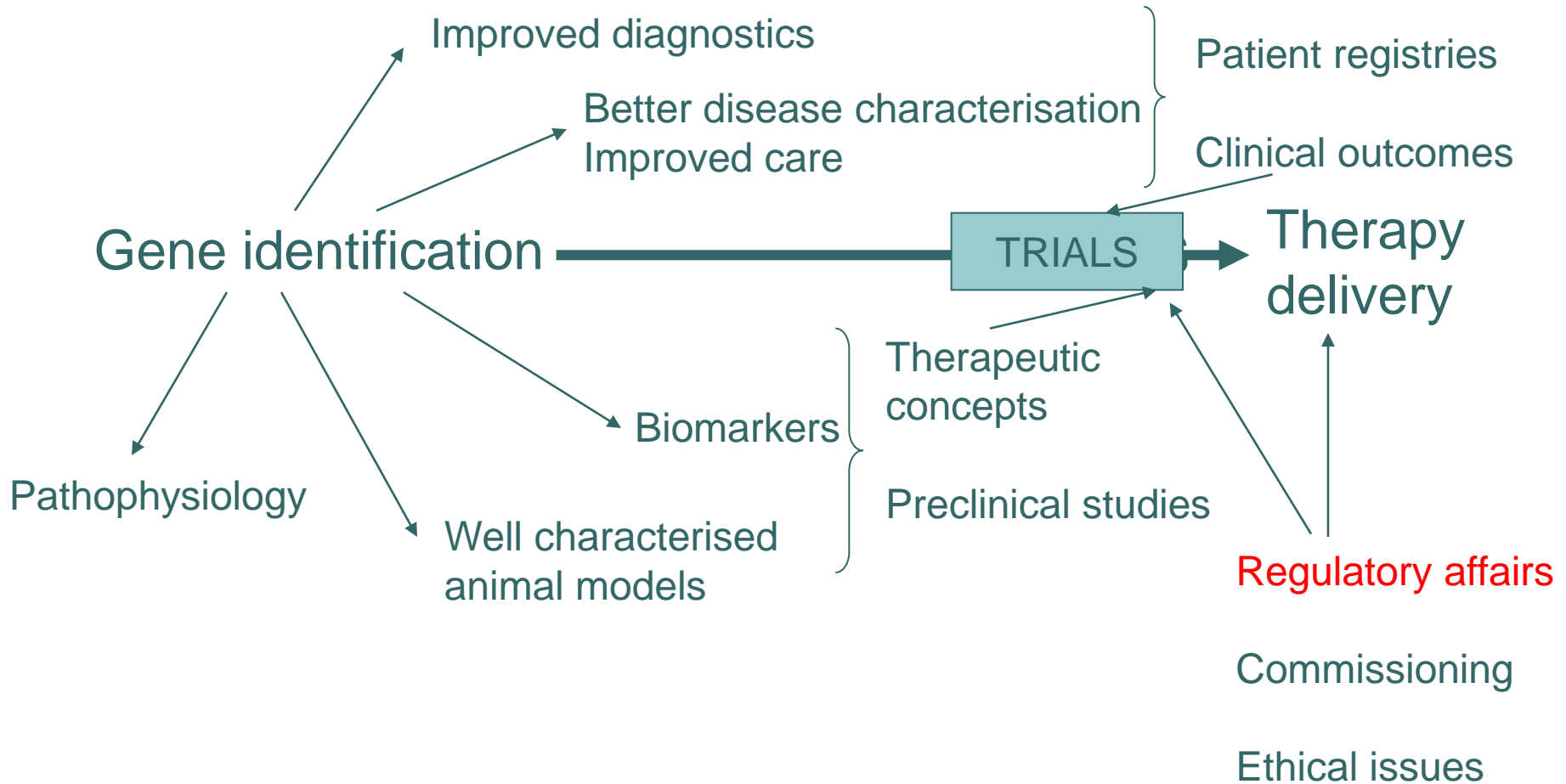
- Who can apply to TACT?
  - **Researcher:** interesting preclinical results on a compound
  - **Clinician:** access to non clinical development know-how
  - **Industry:** to quicker understand the target community
  - **Funders:** review can add value to a proposal and facilitate decision making between opportunities to fund
  - **All groups:** access to advice on clinical trial design, conduct, access to other TREAT-NMD tools and regulatory advice



# TACT experience to date

- Academic and industry applicants
- Projects have moved through the process to develop new funding applications
- Greater involvement of advocacy organisations
- Next meeting: January 2011

# From gene identification to therapy delivery



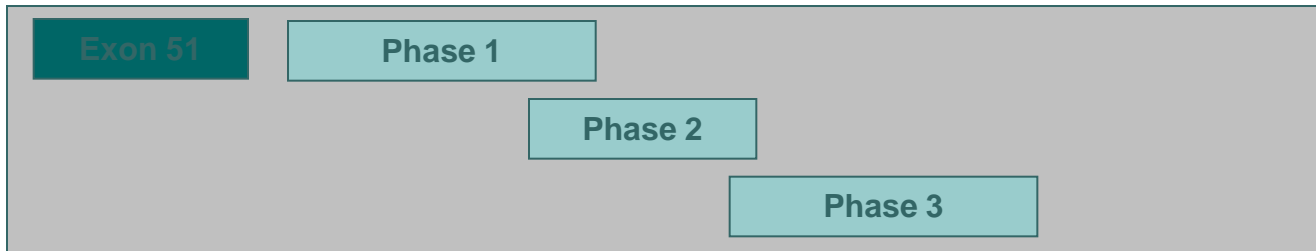
# Personalised medicines: Mutation specific therapies

- Stop codon suppression
  - Multiple diseases, specific mutations
- Exon skipping (DMD)
  - Targeted approach to skip specific exons to restore reading frame

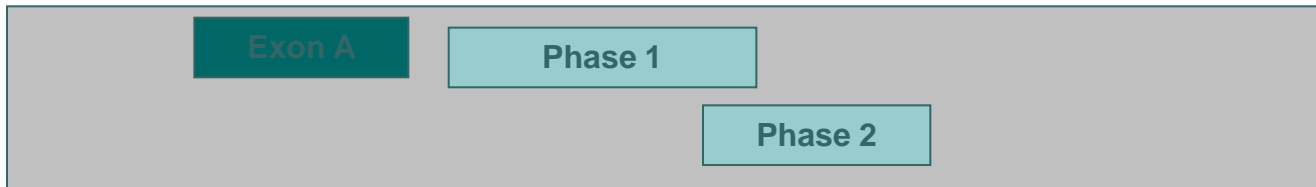
Overview of exons applicable to largest groups of patients

Exon	All mutations	Deletions	Duplications	Small mutations
51	13.0%	19.1%	0.3%	3.0%
45	8.1%	11.8%	0.2%	2.2%
53	7.7%	11.4%	0.1%	1.5%
44	6.2%	8.85	0.4%	2.7%
46	4.3%	6.2%	0.2%	1.6%
52	4.1%	5.7%	0.5%	2.3%
50	4.0%	5.6%	0.2%	1.9%
43	3.8%	5.3%	0.2%	2.6%
6&7	3.0%	3.6%	0.1%	6.3%
8	2.3%	2.3%	0%	8.0%

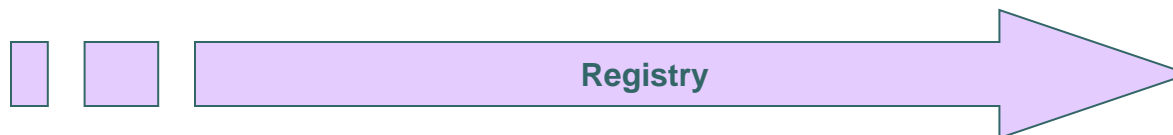
# Exon Skipping Drug Development Paradigm



RCT With  
Clinical  
Endpoint



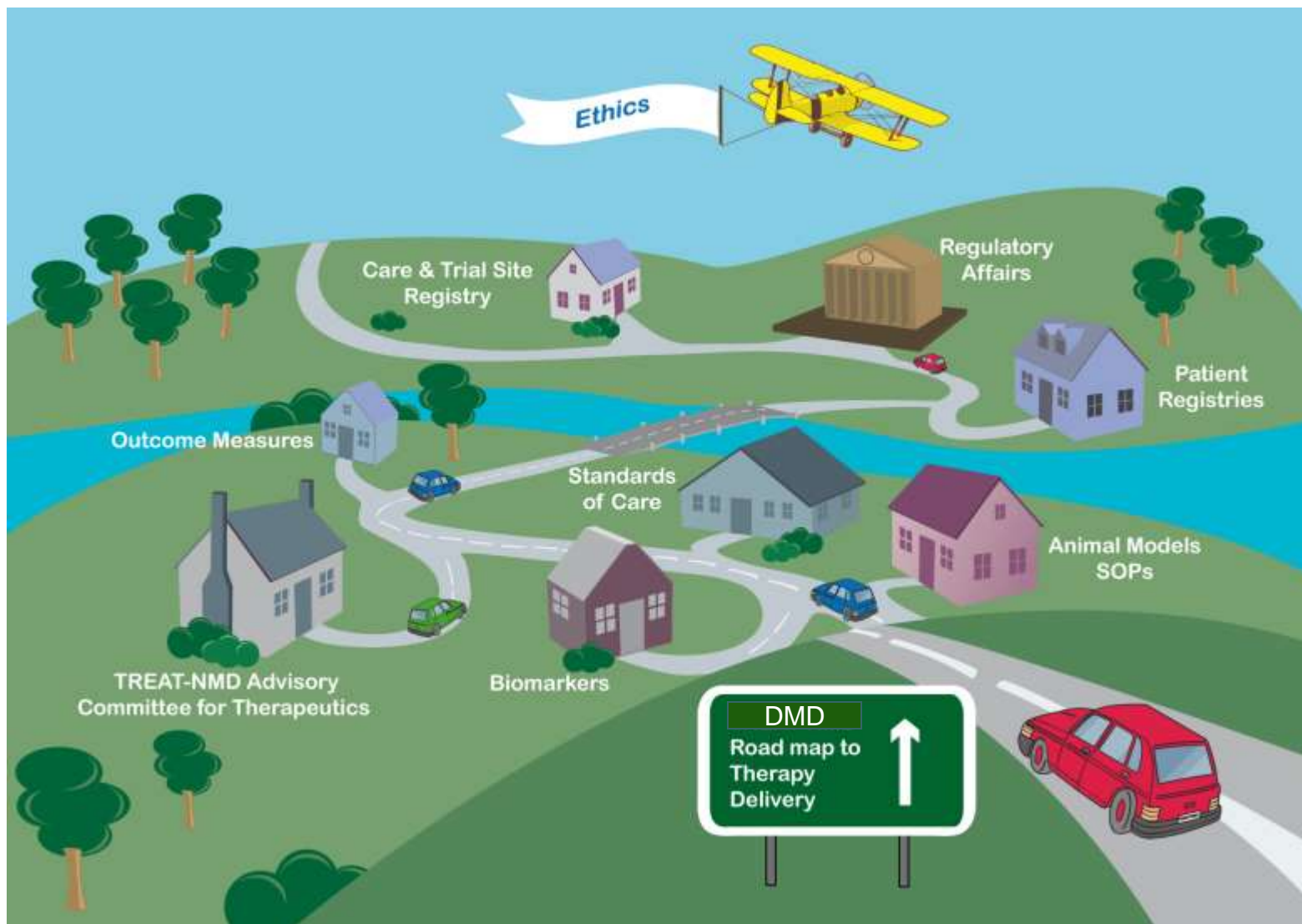
“Surrogate”  
Outcomes



# What are the determinants of success in rare diseases?

- Strong patient organisations driving (and funding) research
- Patient registries
- Strong partnerships
  - Academic
  - Advocacy
  - Industry
  - Regulatory





# Global partners

