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voorzitter stuurgroep weesgeneesmiddelen  
oud voorzitter CBG, voorheen lid CHMP

# Agenda

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- ✓ wat is de stuurgroep
- ✓ knelpunten bij zeldzame aandoeningen
- ✓ Orphan designation
- ✓ waarom is ontwikkeling Orphan Drugs zo lastig
- ✓ post registratie traject

# Stuurgroep weesgeneesmiddelen

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- ✓ adviesorgaan ingesteld door de minister
- ✓ taak
  - positie patiënten met zeldzame aandoeningen te versterken
  - ontwikkeling van Orphan Drugs te stimuleren
- ✓ vertegenwoordiging van alle veldpartijen

# Knelpunten bij therapeutische mogelijkheden

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- ✓ incidentie laag
- ✓ expertise schaars en erg verspreid
- ✓ vaak weinig therapeutische mogelijkheden
- ✓ indien aanwezig komen er meer “lichte gevallen”
  - meer variatie in ernst van de aandoening
- ✓ natuurlijk beloop vaak onbekend
- ✓ nog al eens verschillende moleculaire oorzaak
  - andere factoren bepalen het verloop

## Knelpunten bij trialontwerp

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- ✓ natuurlijk beloop vaak onbekend
- ✓ efficacy bij registratie vaak gemeten aan de hand van surrogaat parameters
- ✓ registratie wegens “unmet medical need”
- ✓ relevante effectiviteit (doelmatigheid) moet nog worden gemeten na registratie
  - hoe
  - wie doet het

# Orhan designation

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## COMP

- ✓ designation op twee pijlers
  - de ziekte moet zeldzaam zijn
  - er zijn aanwijzingen voor toepasbaarheid
  - significant benefit
    - in vergelijking met bestaande therapieën
    - indien na registratie niet kan worden aangetoond, vervalt de Orhan status

# Orhan designation

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## COMP

- ✓ de ziekte moet zeldzaam zijn
  - geen opsplitsing in sub ziekten
  - incidentie < 5 op de 10.000 personen (EU)
  - incidentie < 200,000 mensen in the United States

## Orphan designation

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### COMP

- ✓ free protocol assistance
- ✓ tax reduction in some countries
- ✓ reduction application costs
- ✓ special exclusivity after registration

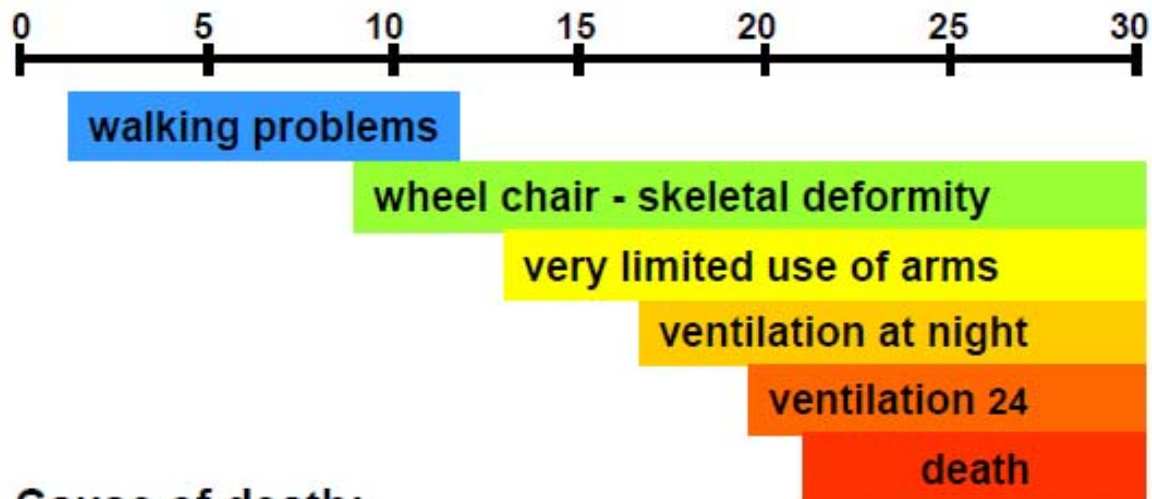
waarom ontwikkeling Orhan drugs zo lastig ?

*Voorbeeld*

*Duchenne's musculaire dystrofie*

relatief frequente erfelijke spierziekte met een incidentie van 1 op 4.000 jongens, d.i. 20 per jaar

- Underlying cause: no dystrophin protein in muscles

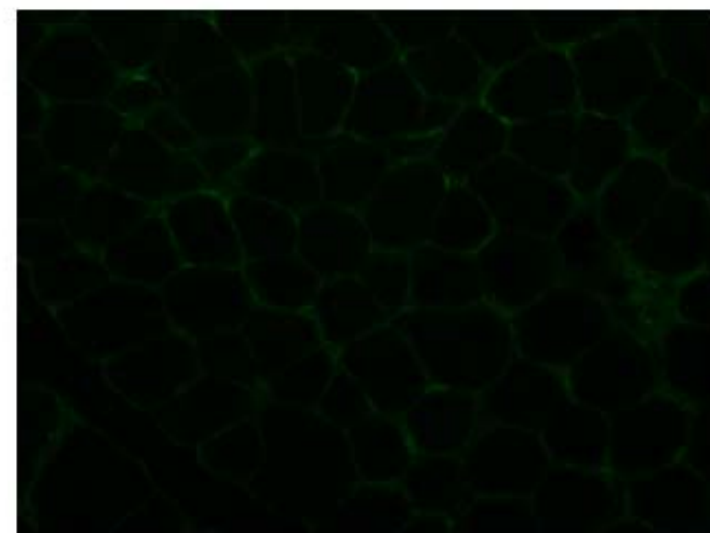
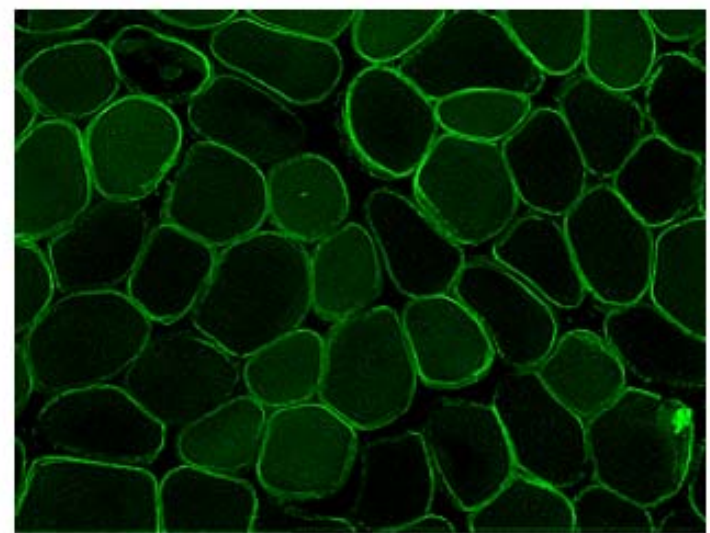
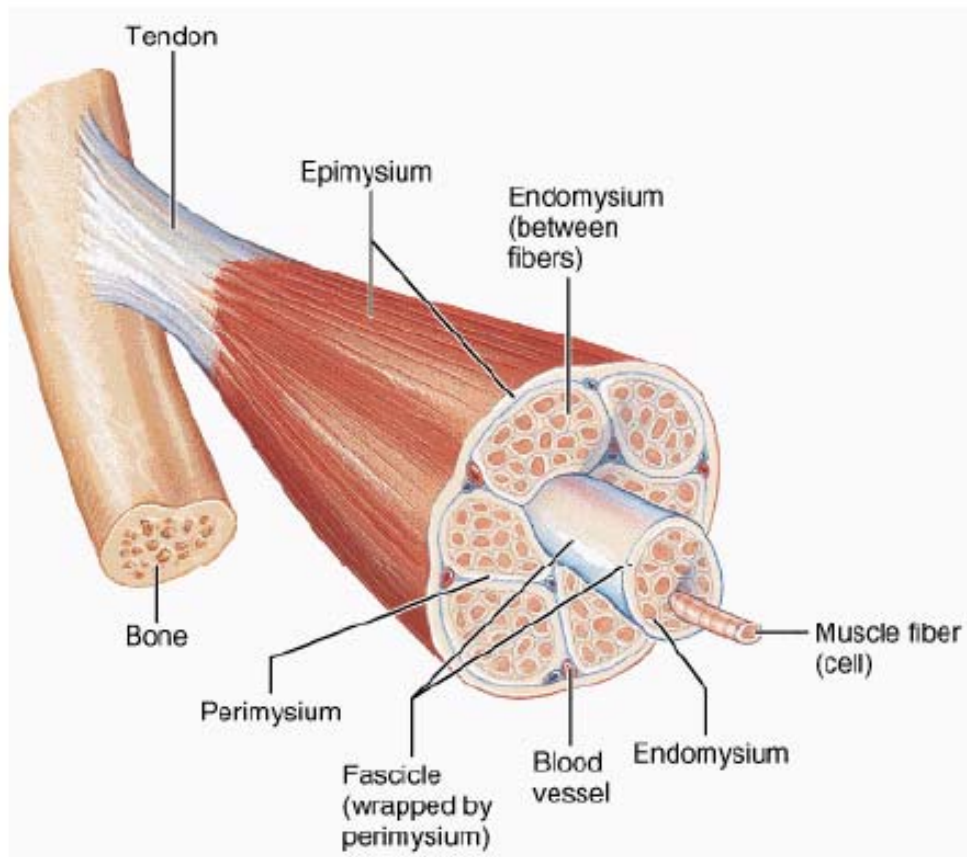


### Cause of death:

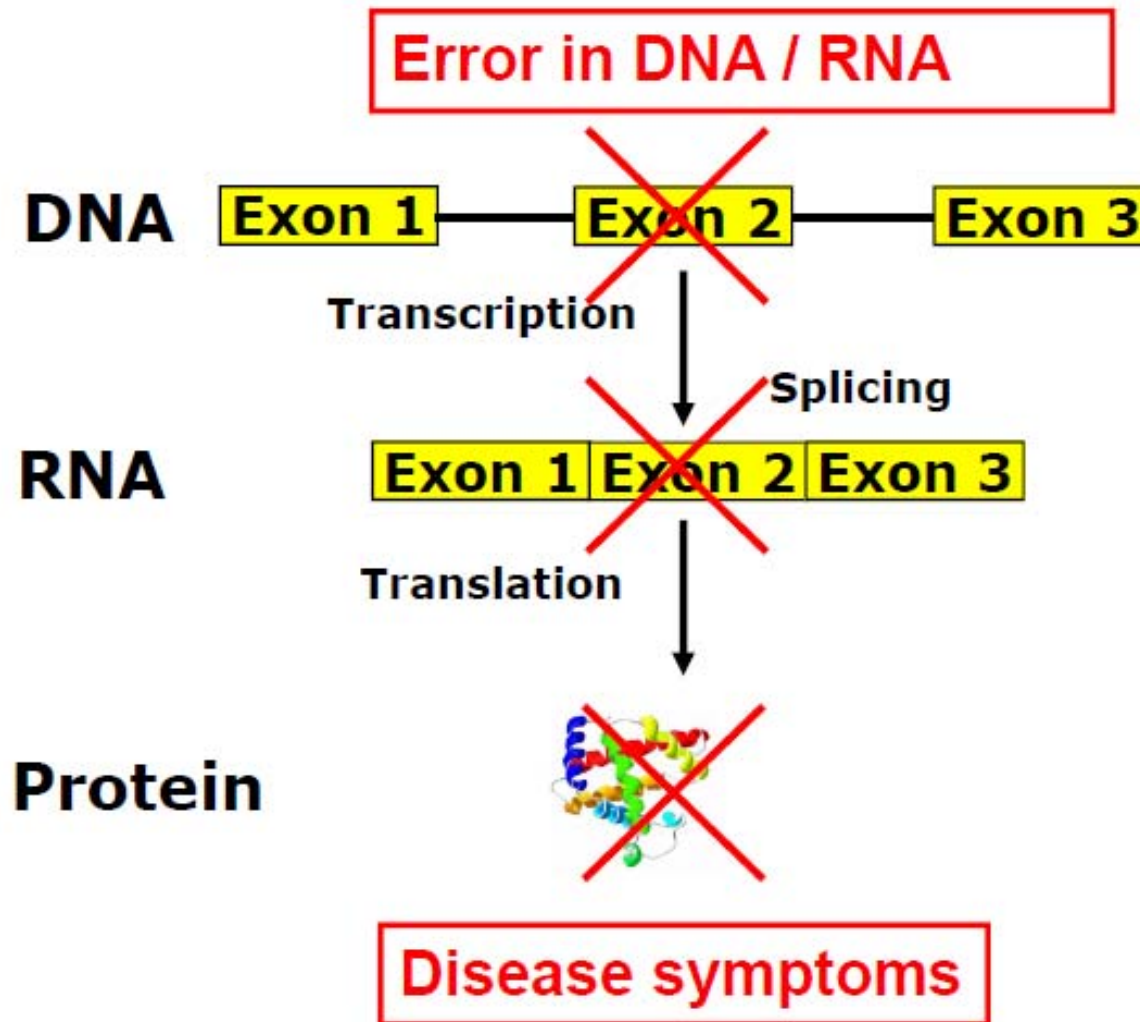
80-90% pulmonary failure / pulmonary infections  
 15% heart failure

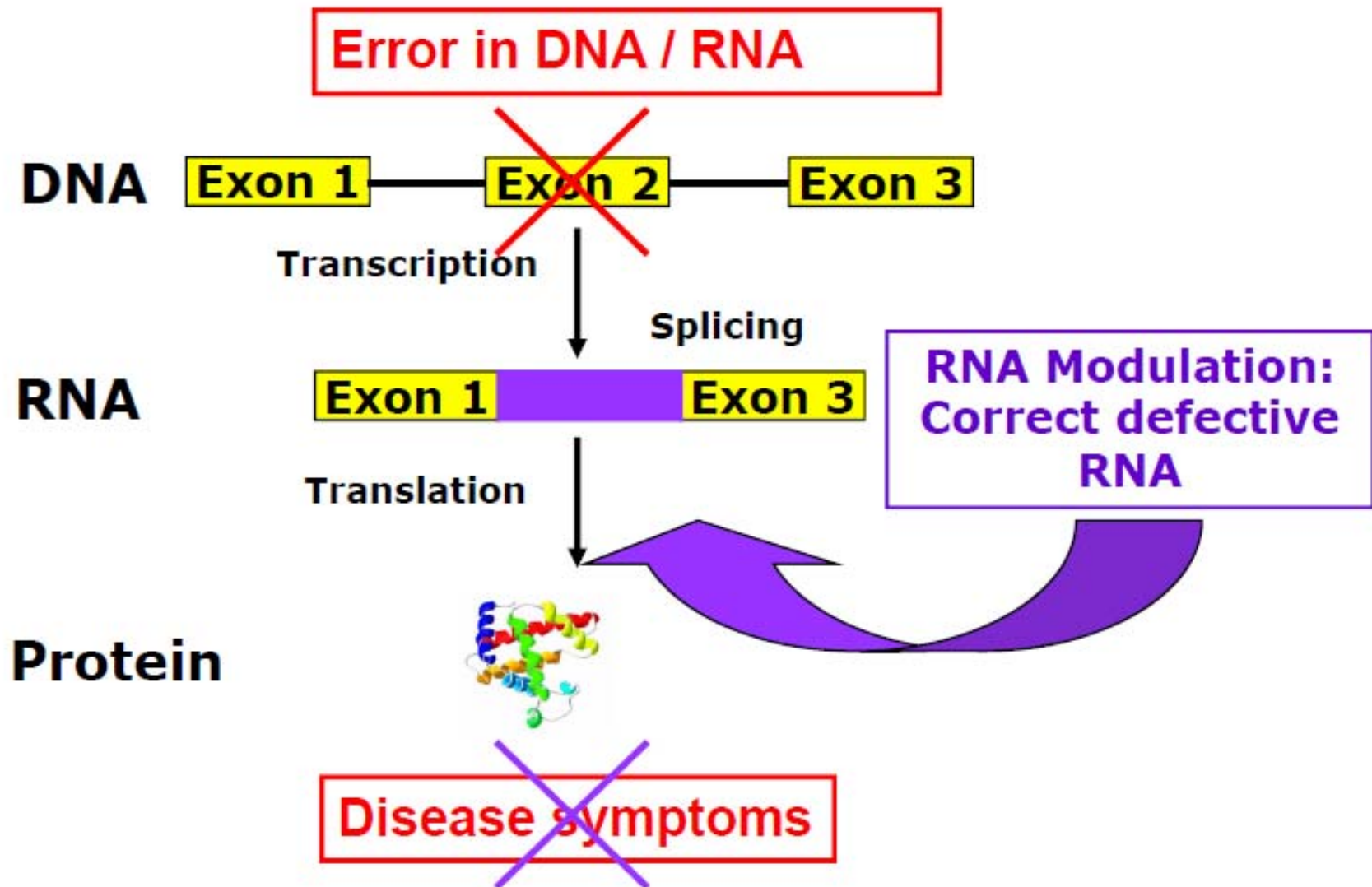


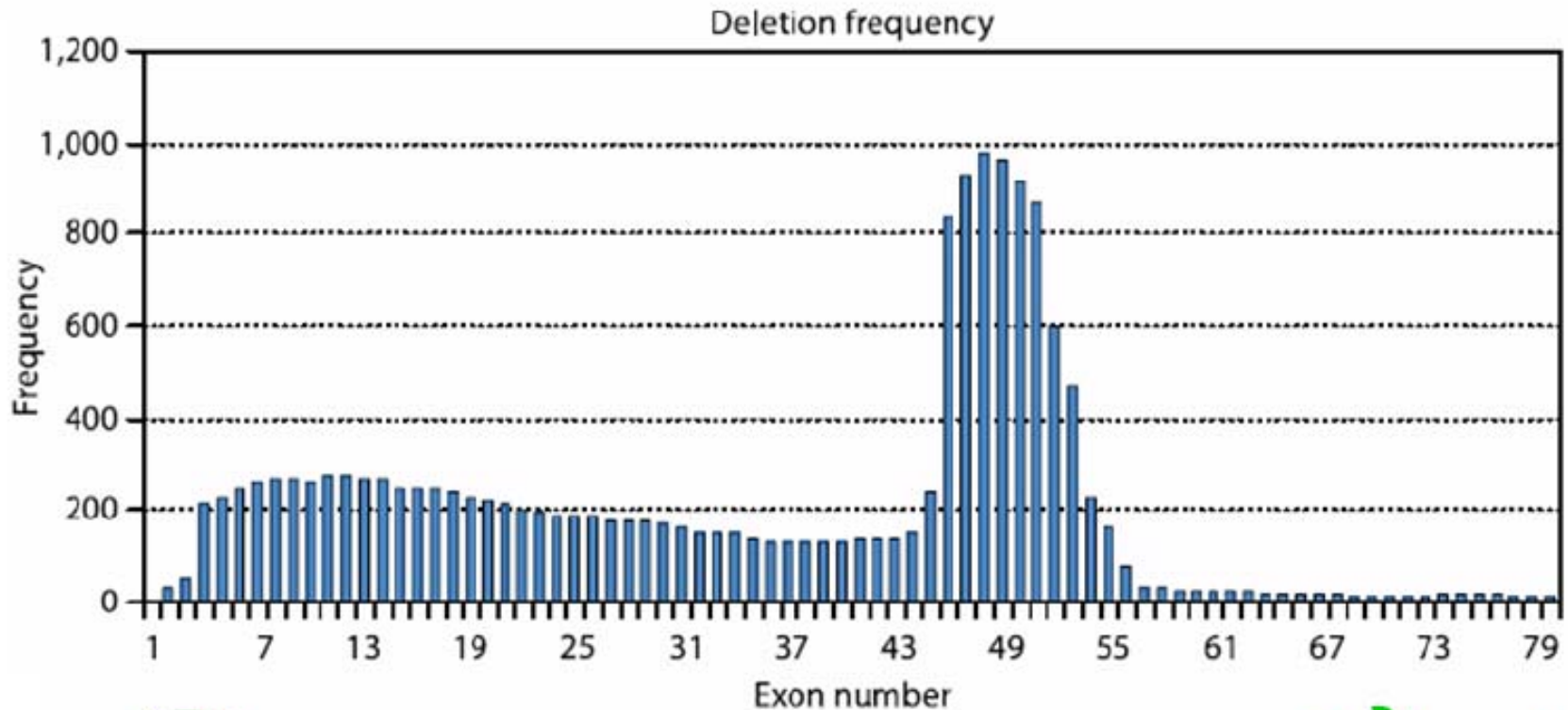
# Duchenne Muscular Dystrophy



te weinig dystrofine rond spiercel







White et al., 2006: Analysis of all deletions (2,609) reported in Leiden DMD database. Shown is number of times each exon is deleted.

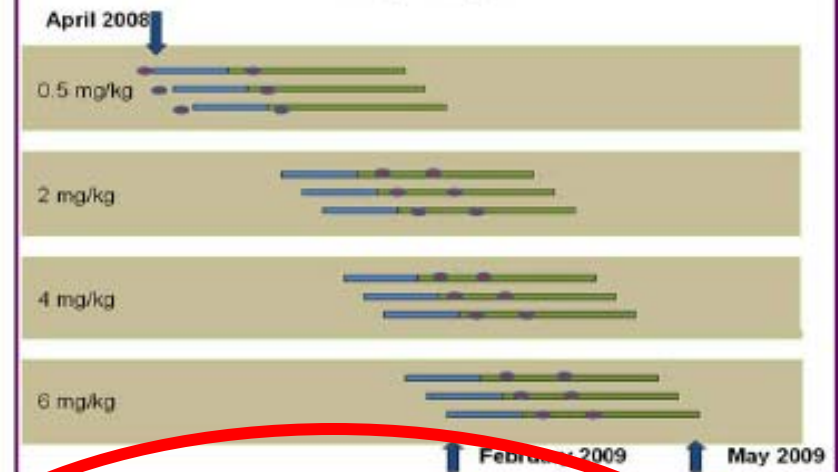
**Design**

- 12 patients / 4 sequential groups (3 patients each);
- 5 weekly **s.c. injections** escalating dose (0.5-2.0-4.0-6.0 mg/kg).

**Analyses**

- Plasma and tissue pharmacokinetic profile;
- Safety parameters;
- Muscle biopsies at two time-points: RNA and protein effects;
- CK levels;
- Muscle strength/performance.

Study design



**Participating sites**

- Leuven, Belgium: Dr Nathalie Goemans
- Gothenburg, Sweden: Dr Mar Tulinius

## Phase 3 trials

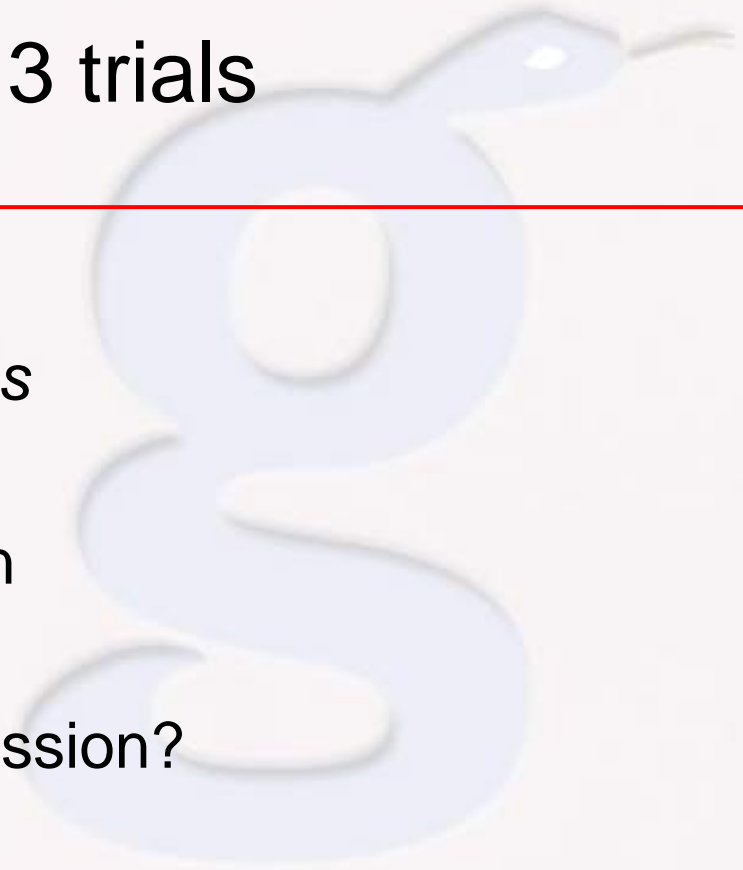
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How to measure efficacy

- ✓ *improvement of symptoms*
- ✓ stopping progression
- ✓ slowing down progression

However

- ✓ what is the natural progression?



## Phase 3 trials

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### How to measure efficacy

- ✓ atypical endpoints
  - 6 minutes walk test
- ✓ more specific endpoints?
- ✓ CTA (clinical trial application) approval

## Phase 3 trials

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### CTA approval

- ✓ phase 1 studies often at national level performed
- ✓ phase 2- 3 trials multicentre multinational
- ✓ EMA / CHMP European trial advice
- ✓ CTA approval process is a national process
- ✓ often delayed approval process
- ✓ discordant decisions

## After registration

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if approval given for exon 46

- efficacy
- safety

what are requirements of other exon skipping products for Duchenne's muscular dystrophy

- efficacy
- safety

## Hoe verder?

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### uitdagingen

- ✓ tijdelijke vergoeding
  - Beleidsregel Weesgeneesmiddelen
  - GVS kent wel permanente vergoeding
- ✓ blijvende vergoeding weesgeneesmiddelen afhankelijk van doelmatigheid studies
- ✓ doelmatigheid studies vaak nationaal
  - patiënten populatie te klein
- ✓ trage besluitvorming om studies te starten

# Feiten

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- ✓ weinig centralisatie van kennis in Nederland / Europa
- ✓ sterke organisatie patiëntengroepen
- ✓ grote bereidheid patiënten organisaties om te helpen
- ✓ *registers van patiënten*
- ✓ *wie beheert zij*
- ✓ *privacy problemen*

*European recommendations of the Council of European ministers of Health*  
8 June 2009

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## **5.11. Registries and databases**

Registries and databases constitute key instruments to increase knowledge on rare diseases and develop clinical research. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological research and/or clinical research.

Collaborative efforts to establish data collection and maintain them will be considered, provided that these resources are open and accessible. A key issue will also be to ensure the long-term sustainability of such systems, rather than having them funded on the basis of inherently precarious project funding

*European recommendations of the Council of European ministers of Health*  
8 June 2009

### 5.11. Registries

Registries and databases provide knowledge on rare diseases, the only way to provide data for epidemiological studies.

Collaborative efforts should be considered, particularly if data are accessible. A key challenge is the sustainability of such registries on the basis of inherent

European databases fashionable:

- 499.8 million\* a generous sample
- funding mechanisms
- ownership

But could be local – national – global

Value of studying the single rare case

are  
size  
will

in the

*European recommendations of the Council of European ministers of Health*  
8 June 2009

## Sustainability

### 5.11. Regi

Registries and  
knowledge  
the only way  
for epidem  
Collaborative  
be consid  
accessible  
sustainabi

“The effort of setting up this registry should not be wasted”

BUT:

1. The reasons for continuing a registry must be as convincing as were the reasons for initially setting it up
2. Maintenance is less sexy than initiation – and harder work

basis of inherently precarious project funding

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## Sustainability

### 5.11

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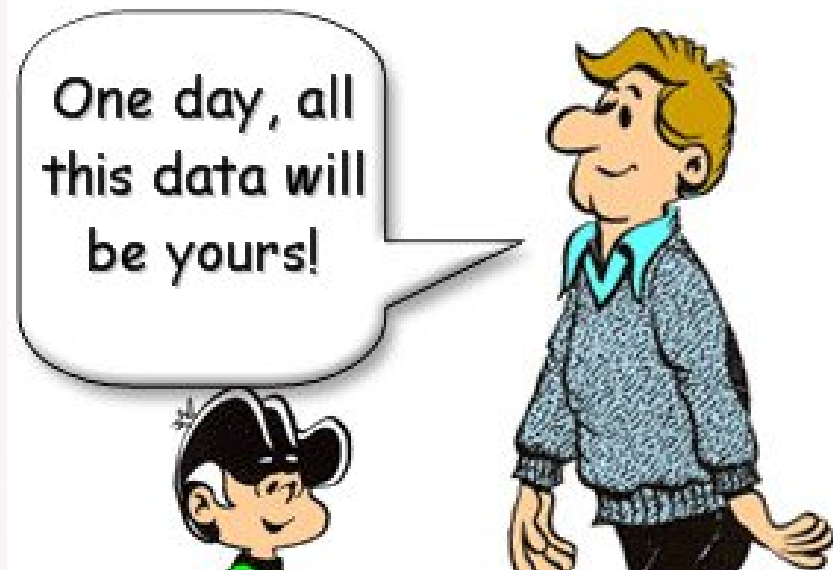
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bas

1. The independence of registries depends more on its governance and funding conditions than on the origin of the funding.
2. Ideally, funding from an interest group will be provided on an unrestricted basis.
3. Industry should consider joining academic-originated registries.
4. Registries should be seen as infrastructures rather than projects,
5. While it is right that funding be time-limited and renewable a mechanism should be found whereby support can be assured to a registry that can show it is properly run, achieving its objectives and has a good reason to continue

*European recommendations of the Council of European ministers of Health*  
8 June 2009

## *Ownership*



The governance of the registry should reflect the concepts of responsibility and custodianship rather than ownership.

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8 June 2009

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## *Governance*

- ✓ All registries should establish the principle of independence in their governance.
- ✓ Registry rules must be public and expressed in simple language, understood by all the stakeholders.
- ✓ Representatives of all the stakeholders should be actively involved in the governance of a registry.
- ✓ The registry must be clearly accountable to its stakeholders.
- ✓ An Oversight Committee should be established; it should protect the interests of patients; it should be independent of industry.

# Conclusies

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- ✓ *klinisch* onderzoek weesziekten in kinderschoenen
- ✓ (post) registratie onderzoek pas zinvol als studies internationaal worden opgezet
- ✓ studies alleen mogelijk bij internationale samenwerking en met expertise centra
- ✓ hulp patiëntenorganisaties onontbeerlijk
- ✓ status registers verdient nadenken
- ✓ financiering, onderzoek, registers