



Leiden University
Medical Center

FISMA for high quality and interoperable real-world data on Dystrophinopathies

FAIR from the start: From concept to reality

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Samen zijn wij LUMC
Together - one LUMC 

Conflict of Interest



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I have no potential conflict of interest to report

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More information?
[Linktr.ee/RWD_NL](https://linktr.ee/RWD_NL)



Duchenne Centre Netherlands (DCN)

Two key figures & fellow authors

- Erik Niks, senior neurologist
- Yvonne Meijer-Krom, coordinator



Duchenne Centre Netherlands (DCN)

- 2 academic centres (Leiden – LUMC & Nijmegen – Radboudumc)
- 1 expertise centre (Heeze – Kempenhaege) for all kinds of neurological learning and developmental disorders, and other brain-related disorders.
- 70% of all Duchenne patients in the Netherlands

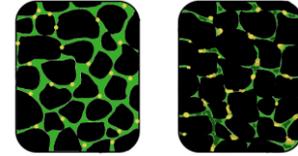
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What is Duchenne Muscular Dystrophy (& Becker)

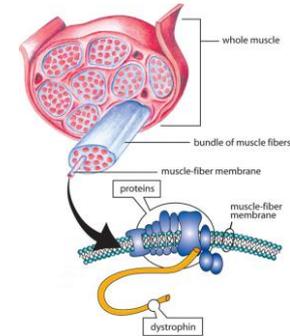
Muscular dystrophies

- Duchenne MD is the most common (50% of all cases)
- Occurrence is around 1 in 3,500-6,000 males
- Since Duchenne & Becker MD involve dystrophin, they are known as dystrophinopathies



Dystrophin

- Largest gene currently know
- Essential for muscle integrity during contraction
- Without dystrophin, skeletal and cardiac muscles sustain continuous damage, leading to loss of functionality



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Duchenne MD is a progressive disease

1st manifestation of muscle weakness:
1,5-3 y/o



decrease in muscle strength: >6-7 y/o

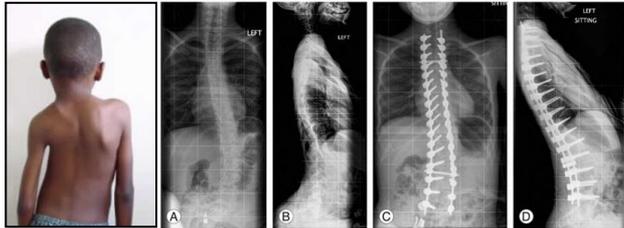
4-6 y/o: Diagnosis

12-14 y/o: loss of ambulancy



scoliosis: 15jr

Loss of muscle strength in arms
>18 y/o : cardiac and respiratory issues



More information?
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Duchenne Centre Netherlands, a key player in NL

- DCN manages the Dutch Duchenne Database (DDD)
- ...and is the instigator for the National Duchenne & Becker Biobank
- ...which is, in turn, part of the LUMC NeuroMuscular Disease Biobank

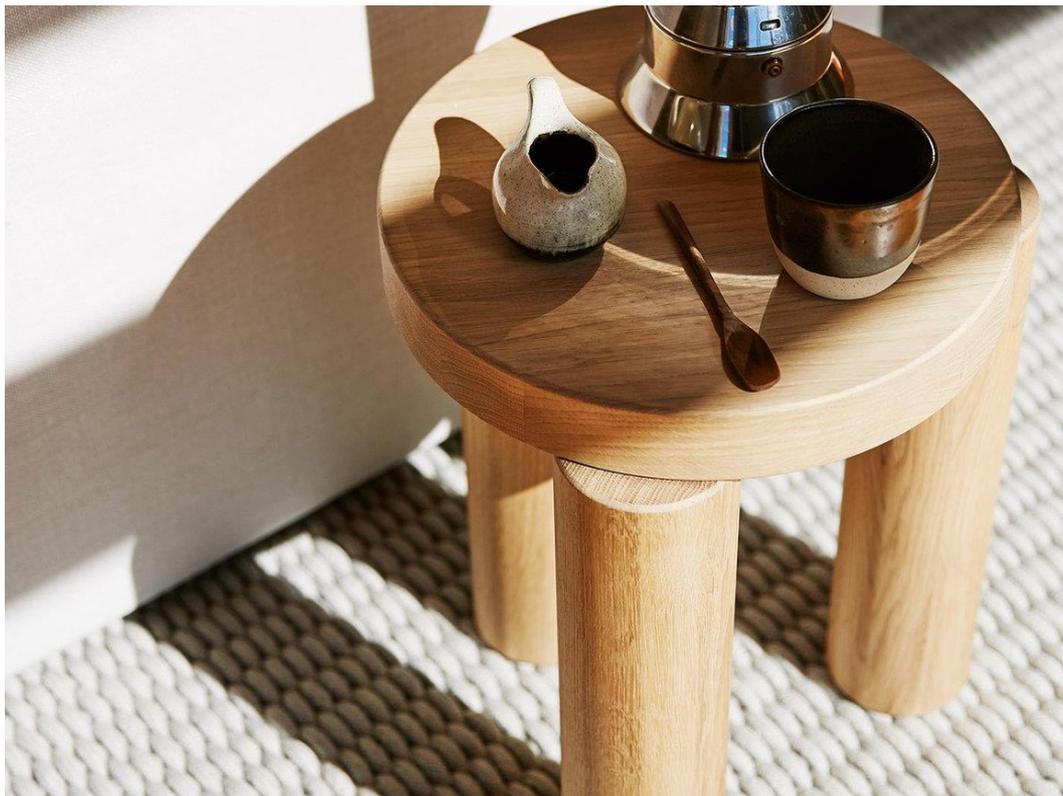
- Until 2018, a traditional approach to data collection placed a huge administrative burden on the organisation, with relatively low coverage

- Thus, FISMA Duchenne & Becker was developed and adopted to address all these issues

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Semantic interoperability (*aka the I in FAIR*)



Is it a stool? Or a side table?

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When (Circulating) Cell-free DNA isn't (c)cfDNA

Scoring evidence challenges after 44 articles – GRADE

Small sample sizes (n<10, 50%)

- No statistics / inconsistency

No uniform approach, e.g centrifuge settings

- 1st centrifuge step 36 unique combinations
- 2nd centrifuge step 32 unique combinations

Underreportage

- Temperature, time, pooled samples (n=2), brakes (n=3)

Outcome measures variation

- Variable extraction methods
- Variable yield/integrity/mutation measurements

| 1st centrifugation step combinations |
|--------------------------------------|
| 300g 20m |
| 380g 20m |
| 800 g 10m |
| 800g 10m |
| 820g 10m 4d |
| 820g 10m RT |
| 900g 7m RT |
| 1300g |
| 1300g 20m RT |
| 1350g 12m |
| 1370g 10m 4d |
| 1500g 10m |
| 1500g 10m RT |
| 1600g 10m |
| 1600g 10m 4d |
| 1600g 10m RT |
| 1600g 15m RT |
| 1600g 20m |
| 1600g 20m RT |
| 1700g 10m |
| 1700g 5m |
| 1900g 10 |
| 1900g 10m 4d |
| 1900g 7m |
| 2000 rpm 15m 4d |
| 2000g |
| 2000g 10m |
| 2000g 10m 4d |
| 2000g 10m RT |
| 2500 rpm 10m 4d |
| 2500g 10 |
| 2500g 10m 4d |
| 2500g 10m RT |

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FISMA is born

- Framework for **I**nformation **S**pecification, **M**odelling, and **A**rchitecture

Primary principles

- Registration and *curation at the source*
- Reusability – register once, use many times for all purposes
- Ontology-based
- Context is key!

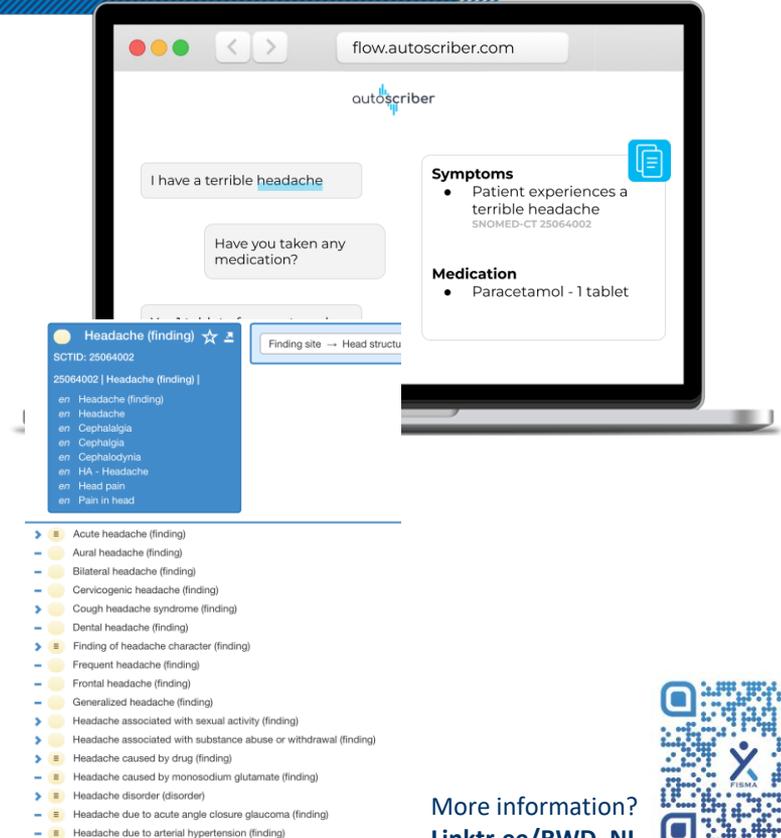
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What FISMA *isn't*

FISMA is never

- Obtrusive
- a registration burden
- a goal in itself
- FISMA is based on multiples, not triples
- We don't believe in post-hoc *curation*



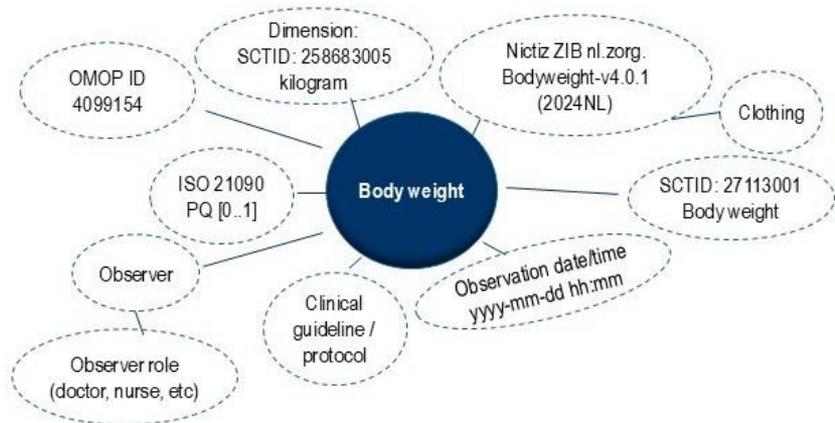
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FISMA - every element richly embedded

FISMA

Example of data element embedded in metadata



Clinical guidelines
Standards of Care

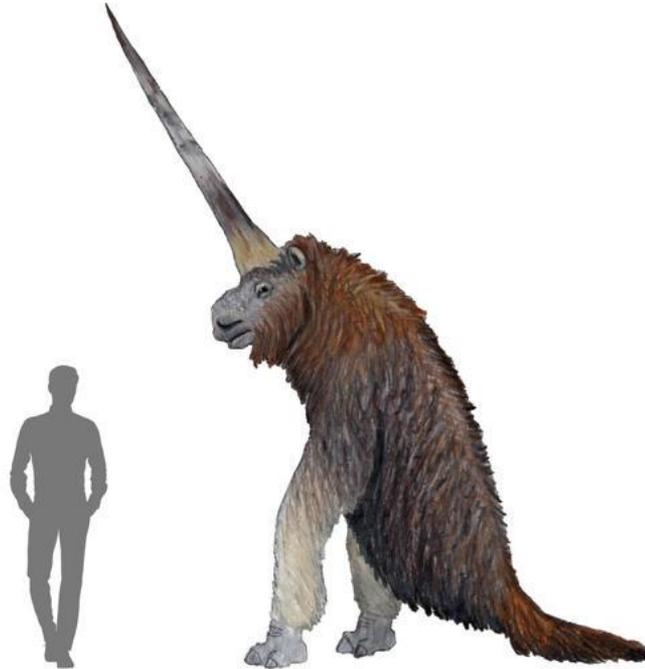
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A biobank sample is like a modern fossil

Magdeburg unicorn

Gottfried Wilhelm Leibniz



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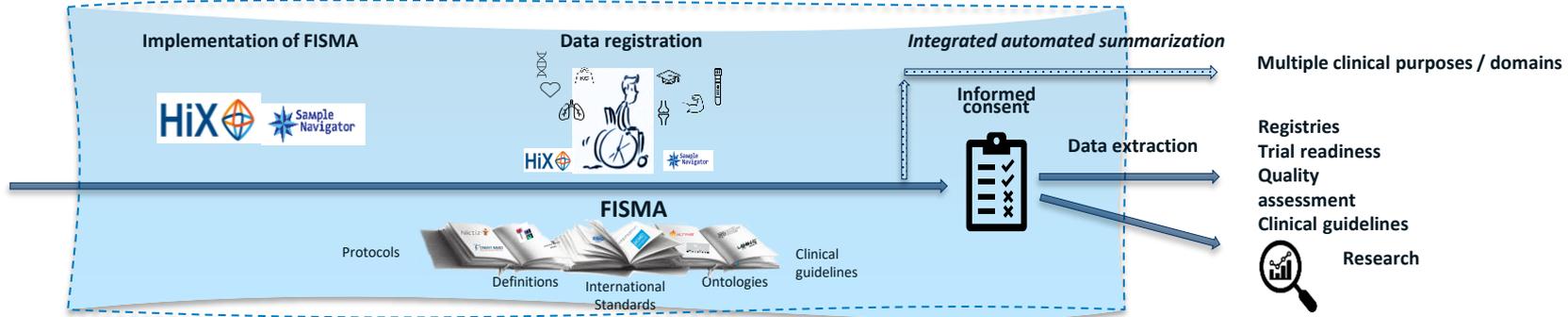
FISMA principles applies to biomaterials (*draft*)

| Element | Definition | Value (domain) (<i>example</i>) | Coding | Cardinality requirement | Note |
|---|--|---|---|-------------------------|--|
| ID of participant | | | data type II | 1 | |
| Cohort | local descriptor collection or study | REMICADEPIB4002: A multicentre, prospective, long-term registry of paediatric patients with Crohn's disease: an EU-specific registry protocol (zie ook P10.0XX) | data type ST OID (https://www.hl7.nl/actuele-hi7-nl-oid-register.html) | 0..1 | Meta information , may be implied by cohort/protocol |
| Centre of collection | hospital where material is collected | LUMC OLVG endoscopy centre etc | OID (https://www.hl7.nl/actuele-hi7-nl-oid-register.html) | 1 | Meta information for centre |
| Date/Time of collection | Date/Time when material was extracted from participant | 23-01-2023 11:30 GMT | date time + timezone | 1 | |
| Specimen | | | | 1..N | |
| Unique ID of specimen | | | data type II | 1 | where status of material <> |
| ID of parent specimen | | | data type II | 0..1 unprocessed | |
| Status of material | Derived from protocol (collection protocol or processing protocol) | raw/unprocessed processed | derived | 1 | Pseudo-element |
| Centre (or lab) of processing | centre/ lab where material is processed | LUMC OLVG endoscopy centre etc | OID (https://www.hl7.nl/actuele-hi7-nl-oid-register.html) | 1 | Meta information for centre |
| Date/Time of processing | Start date/Time when material was processed according to protocol | 23-01-2023 11:30 GMT | date time + timezone | 1 unprocessed | where status of material <> protocol may call for additional date/Time stamps as observations |
| Date/Time of storage | Start date/Time when material was stored according to protocol | 23-01-2023 11:30 GMT | date time + timezone | 1 unprocessed | where status of material <> protocol may call for additional date/Time stamps as observations |
| Type of material | material as collected / processed | [Venous]arterial[capillary] blood tissue biopsy CSF Synovial fluid etc | Snomed CT | 1 | may be derived from protocol, CD to be provided at a later date |
| Body site of material | location of collection on body as macroscopically assessed by relevant health professional | Structure of palm of left hand (body structure) SCTID: 789216008 Descending colon structure (body structure) SCTID: 32622004 | Snomed CT | 1 unprocessed | where type of material <> blood AND where status of material = may be derived from protocol |
| Nature of material | | healthy diseased malignancy neoplasm inflamed etc | Snomed CT | 0..1 | |
| Indication for collection | working diagnosis, procedure, in accordance with cohort protocol etc | ##### | ID in Diagnosis, Treatment, or both | 0..1 | Meta information , may be derived from protocol (eg biopsy of malignancy during mastectomy) |
| collection consumable, descriptor | the container used to collect/store material | EDTA, 9 ml | Snomed CT | 1 | may be derived from protocol |
| collection consumable reference | reference to entry in consumables repository | ##### | | 0..N | may be derived from protocol |
| Protocol | protocol used for collecting / processing material | ##### | ID in protocol repository | 1 | may be supplied in study protocol |
| protocol deviations / observations | | | | 1..N | |
| Date/Time of observation / deviation | Date/Time when material when an observation was made / deviation was reported | 23-01-2023 11:30 GMT | date time + timezone | 1 | |
| observed / deviated element | protocol element where deviation was observed / observation was made | ##### | dependent on protocol repository | 1 | coding is proprietary, based on protocol repository |
| deviation | value of deviation / observation | TBA | PQ / Num / INT | 1 | coding is proprietary, based on protocol repository |
| end protocol deviations | | | | | |
| End Specimen | | | | | |

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FISMA governs every step of the process



FISMA allows extraction of structured data from HiX Duchenne and Becker MD

- Length, weight, BMI
- Lab results
- Disease milestones (eg loss of ambulence)
- Genetics on DMD mutation
- Cardiac data (eg ECG)
- Lung assessments (eg forced vital capacity)
- Muscle function and strength (eg physiotherapeutic assessments)
- Social anamnesis (eg employment)
- Spine assessments (eg scoliosis)
- Bone health (eg osteoporosis)

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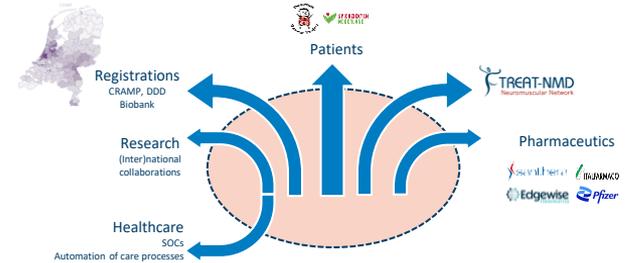
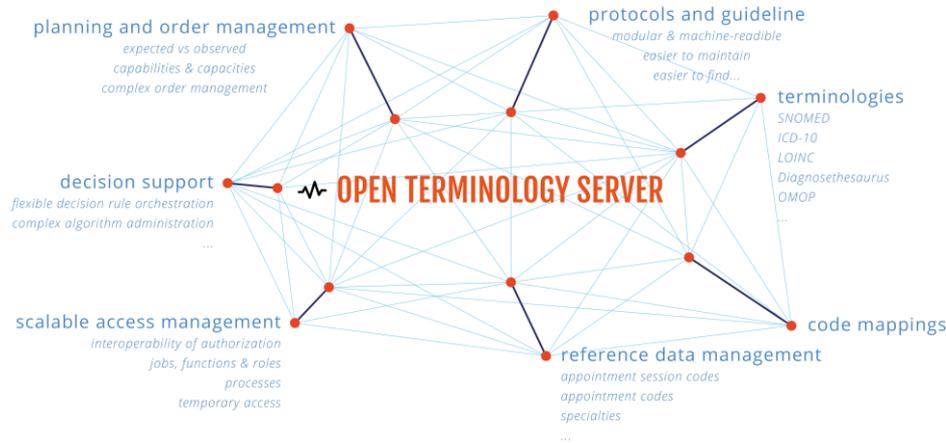


Open Terminology server – the key to multiples

OPEN TERMINOLOGY SERVER

not just the data, also its meaning
a one-stop-shop for knowledge

a one-stop-shop for all types of knowledge, presented in a scalable and machine-readable form, making knowledge available for all applications.



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