Estimation of direct non-reimbursable medical costs, direct non-medical costs and indirect costs of patients with Duchenne de Boulogne disease in France

CouDuMyo

Sponsor: AP-HP

Investigator coordinator: Pr. Isabelle DURAND-ZALESKI

ABSTRACT

TITLE	Estimation of direct non-reimbursable medical costs, direct non-medical costs and indirect costs for patients with Duchenne de Boulogne disease in France. 'CouDuMyo'
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VERSION DU PROTOCOLE	1.3 du 12/01/2023
VERSION DU RÉSUMÉ	1.2 du 15/11/2022
JUSTIFICATION / CONTEXTE	Duchenne muscular dystrophy (DMD) is a chronic neuromuscular disease affecting around 150 to 200 newborns per year, characterized by progressive muscle atrophy and weakness caused by complete dystrophin deficiency. DMD has a severe phenotype, with death most often occurring in the 3rd decade. Very little data is available on the use of care and associated costs for DMD patients, particularly in the context of care in France. A protocol to study the care pathway of these patients using data from the Banque nationale des données maladies rares (BNDMR) and the Système national des données de santé (SNDS) has been proposed by AP-HP (EPARDYS). It will be used to describe patient characteristics, healthcare utilization and associated costs. With regard to the latter, only direct costs eligible for reimbursement (Affection Longue Durée 100%) can be analyzed. The aim of the project is to meet the expectations of HAS and CEPS by providing medico-economic data for the evaluation of the gene therapy product currently being developed by Pfizer (fordadistrogene movaparvovec - PF-06939926). Clinical development began with a phase 1b trial (NCT03362502); a phase 3 trial is currently being recruited for ambulatory patients aged 4 to 7 years (NCT04281485), and a phase 2 trial (NCT05429372) for patients aged ≥2 to <4 years. However, other resources are consumed by DMD patients, notably for their medical care, and are not eligible for reimbursement. What's more, the patient's level of dependence may mean that he or she has to make adjustments or incur other expenses outside the health sphere, but linked to the pathology. Finally, informal help can be very important. All these family costs need to be estimated.
OBJECTIVES	A protocol to study the care pathway of DMD patients using data from the Banque nationale des données maladies rares (BNDMR) and the Système national des données de santé (SNDS) has been proposed by AP-HP (EPARDYS). It will be used to describe patient characteristics, healthcare utilization and associated costs. With regard to the latter, only direct costs eligible for reimbursement (Affection Longue Durée 100%) can be analyzed. Numerous studies show that the cost of managing Duchenne disease must take into account not only direct medical costs, but also non-medical costs, including informal assistance, and indirect costs, which represent a significant proportion from a societal perspective. There is very little information available in France, so this assessment is relevant

	in view of the development of new treatments that could substantially alter the nature of these costs. In this study, we are interested in estimating all the relevant expenditure items from society's point of view, taking into account patients who are minors as well as adults who may have a professional activity. The medico-social aspect and the collection of aid and benefits received will also provide an insight into the nature of the support available to French families. • **Research hypothesis** In addition to the EPARDYS study of direct reimbursed medical costs, the aim of this study will be to carry out a specific analysis that takes into account the other costs associated with the management of the pathology, i.e., the direct costs of the healthcare sphere not eligible for reimbursement, the medico-social sphere and the domestic sphere, as well as the indirect costs associated with lost productivity. • **Main objective** Décrire les consommations de ressources liées à la prise en charge des patients atteints de DMD en dehors de celles éligibles au remboursement, c'est-à-dire en termes de : coûts directs médicaux non éligibles au remboursement et médico-sociaux, coûts directs non médicaux et coûts indirects. • **Secondary objectives** - Estimate the different types of costs identified for pathology management; - Estimate costs as a function of disease severity; - Describe the cost drivers identified
METHOD	This is a national, cross-sectional, non-comparative, sample-based cost analysis survey. Insofar as this study does not study the pathology itself, nor intervene in its management, it corresponds to research not involving the human person.
CRITERIA	• **Main criterion** Average annualized cost per patient/family. • **Secondary criteria** - Average annualized cost by type of cost and by patient/family. - Average annualized cost per patient/family for each stage of disease severity. - Cost drivers identified.
POPULATION	This study will focus on DMD patients of all ages included in the BNDMR. This database gathers data on all patients treated in the Centres experts maladies rares (CERDs) accredited by the DGOS, and shows a gross number of 2,028 DMD patients as of March 1, 2022.
INCLUSION CRITERION	- Patients of any age with DMD diagnosed more than 6 months ago; - Patients included in the BNDMR, who do not object to their data being collected, and who are alive at the time they are asked to take part in the study.
NON-INCLUSION CRITERION	- Patient participating in an interventional clinical study with modification of usual care; - Patient and/or primary caregiver objecting to the use of his/her data; - Patient and/or primary caregiver whose comprehension of the French language does not allow them to complete the questionnaire.
STUDY EXIT CRITERIA	Subjects may object to their participation and ask to leave the study during the interview, for whatever reason. In the event of premature exit (questionnaire not fully completed), and if the subject does not object, the data collected up to the point of objection will be analyzed.

PROCEDURES	A standardized questionnaire will be sent to patient/caregiver couples with the information letter. A clinical research associate will then contact the patient and/or primary caregiver by telephone. The interview (30 minutes maximum) will be based on the questionnaire, and will ensure that the participant(s) have understood the questions and that all the required data have been collected.
RATIO BENEFIT/RISK	This is a descriptive study, the aim of which is to analyze the costs borne by patients and their caregivers, as well as the costs associated with informal help, in the context of DMD management in France. No individual benefit is expected from participation in this study, which will contribute to improving knowledge of the various expenses associated with the disease. The only constraint for participants will be to answer a questionnaire. Overall, the benefit/risk balance for the privacy of patients and families is therefore acceptable.
SUBJECTS NUMBER	The sample size for 15% accuracy is 171 patient/caregiver pairs according to the recommendations of Johnston et al. 2019.
STUDY DURATION	Inclusion period: 6 months (01/2023 - 06/2023) Duration of participation for each subject: completion of questionnaire (30 minutes max) Total study duration: 6 months (01/2023 - 06/2023)
RESEARCH SITES	All French centers accredited by the DGOS and providing the usual care for DMD patients, and contributing to their registration in the BNDMR.
EXPECTED BENEFITS	- For patients and their carers: find out what patients and carers consume in connection with the disease, identify the most significant expenditure items, contribute to the development of the HAS ALD guides. - For HAS and the Comité Economique des Produits de Santé (CEPS): identify and quantify expenses associated with the disease in the absence of specific treatment. Knowledge of disease-related consumption (excluding direct medical costs) as a function of patient characteristics complements the EPARDYS study's collection of direct medical costs. It will thus provide a complete picture of Duchenne-related expenses borne by patients and caregivers in France.

LIST of ABBREVIATIONS

ALD	Affection Longue Durée
AP-HP	Assistance Publique Hôpitaux de Paris
BNDMR	Banque Nationale de Données Maladies Rares
CEPS	Comité Economique des Produits de la Santé
DGOS	Direction Générale de l'Offre de Soins
DMD	Dystrophie Musculaire de Duchenne
DPO	Data Privacy Officer - Délégué à la protection des données
DRCI	Direction de la Recherche Clinique et de l'Innovation
DSI	Direction des systèmes d'information
DSN	Direction des Services Numériques
HAS	Haute Autorité de Santé
MDPH	Maison Départementale des Personnes Handicapées
PNDS	Protocoles Nationaux de Diagnostic et de Soins
SNDS	Système National des Données de Santé

CONTENT

1. GENERAL INFORMATION

1.1.1 Investigators

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The investigators also form the study's scientific committee.

1.2 Associate scientists

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1.4 Financing

The funding body is the Pfizer laboratory, and funding is the subject of a contract between Pfizer and AP-HP.

2 SCIENTIFIC RATIONALE

2.1 Current state of knowledge

Background to the study

Duchenne muscular dystrophy (DMD) is a chronic neuromuscular disease affecting around 150 to 200 newborns per year, characterized by progressive muscle atrophy and weakness caused by complete dystrophin deficiency. DMD has a severe phenotype, with death most often occurring in the 3rd decade.

Muscular weakness begins with damage to the lower limbs, then the back and upper limbs, leading to progressive loss of the ability to walk, which occurs on average in early adolescence. As the disease progresses, damage to the respiratory, cardiac and digestive muscles leads to other disorders affecting the patient's life. Other disturbances may also be observed, such as emotional disorders, learning difficulties or episodes of anxiety and depression. Relatives (or informal caregivers) are therefore heavily involved in the day-to-day management of the consequences of the pathology.

Patients are currently cared for within the Filnemus rare disease network, via reference and competence centers. Treatment (based on daily corticosteroids, cardioprotective drugs, regular physiotherapy, respiratory physiotherapy and spinal arthrodesis1) has improved life expectancy over time. Over 90% of children with DMD now reach adulthood, and some now live beyond the age of 401. New treatments, such as gene therapies, are currently in clinical development for this disease, with a major potential impact on current management and the organization of care.

Very little data is available on the use of care and associated costs for DMD patients, particularly in the context of care in France. The AP-HP has proposed a protocol to study the care pathway of these patients, using data from the Banque nationale des données maladies rares (BNDMR) and the Système national des données de santé (SNDS). It will be used to describe patient characteristics, healthcare utilization and associated costs. With regard to the latter, only direct costs eligible for reimbursement (Affection Longue Durée 100%) can be analyzed.

However, other resources are consumed by DMD patients, notably for their medical care, and are not eligible for reimbursement. What's more, the patient's level of dependence may mean that he or she has to make adjustments or incur other expenses outside the health sphere, but linked to the pathology. Finally, informal help can be very important. All these family costs need to be estimated.

Summary of the literature on non-medical direct and indirect costs

A total of eight scientific publications studying the costs of informal care and/or indirect costs related to Duchenne Muscular Dystrophy (DMD) were identified following a keyword search in the PubMed database (see Table 1). These were cross-sectional studies published between 2013 and 2022, based on the use of questionnaires specifically developed for collecting relevant resources. The questionnaires were self-administered, except for the study by Labisa et al. [1], which conducted face-to-face interviews.

Five studies estimated the overall cost of the disease from a societal perspective; they included direct medical and non-medical costs, including informal care (except for Larkindale et al.) [2], and indirect costs related to the loss of productivity of the main caregiver and/or the patient. One study estimated only the direct medical and non-medical costs borne by the family (Flores et al.); and one study focused solely on indirect costs, estimated based on the loss of productivity of the main caregiver in a population of minor patients [3].

Despite differences in populations and methods of collection and valuation, the study results were consistent. Overall, the most significant expense categories included: costs related to disability aids and home/vehicle modifications; informal care costs; and indirect costs. These costs increased with the severity of the disease, particularly regarding the patients' ambulatory status.

Regarding studies that estimated informal care costs, the valuation of hours provided by caregivers was conducted using the replacement cost method ("proxy good method"; [1,4,5]) or the human capital approach [6,7]. Informal care costs represented a substantial portion of the total cost of the disease: 18% to 31% for Landfeldt et al.; 27% for Schreiber Katz et al.; and 42% to 50% depending on the patients' ambulatory status for Labisa et al.

[1] Protocole de diagnostic et de soins (PNDS) – Dystrophie musculaire de Duchenne – HAS – novembre 2019

Cavazza et al. based their estimation on a population from 8 European countries between 2011 and 2013, where 70% of the affected patients were under 17 years old. The authors estimated that non-medical direct costs represented between 64% and 89% of the estimated total cost, depending on the country, with informal care costs being the main contributor (7 out of 8 countries). In France, non-medical direct costs accounted for 66% of the total cost, and informal care costs for 57% of the total cost (€33,400 and €58,700, respectively, in 2012), but only 2 patients were involved. Differences between the studied countries were attributed to each society's choices, particularly regarding support for families.

Schreiber-Katz et al. reported that 89% of the surveyed patients required a full-time or part-time caregiver (the study population included patients aged 1 to 42 years, with the number of patients over 18 not specified in the publication). The study by Flores et al. surveyed caregivers of minor patients, 52% of whom were under 7 years old [8]. Overall, 70% of caregivers reported not using professional help. The cost of informal care was not valued.

Teoh et al. reported a high cost related to formal care, accounting for 26% of the total cost, in contrast to a low share of informal care costs; however, this valuation did not include the main caregiver, but rather other sources of help (friends, neighbors...).

The valuation of indirect costs was carried out in 4 studies using the human capital approach based on the Work Productivity and Activity Impairment Questionnaire or WPAI [1,4,6,7]. Schreiber-Katz et al. estimated indirect costs based on the salary of the respondent; and Larkindale et al. modeled the loss of family income related to the pathology.

Only one study accounted for the loss of productivity of both caregivers and adult patients [5], while others estimated only that of caregivers [1-3,6]. Cavazza et al. analyzed only the loss of productivity of adult patients, but the number of respondents was too low for a meaningful estimate.

Larkindale et al. estimated an annual income loss for families of $15,481 (2010 value), accounting for 30% of the total cost. In the study by Landfeldt et al. conducted between 2012 and 2013, indirect costs were the largest component of the total cost of the disease in Germany, Italy, and the USA ($20,770, $18,220, and $21,550, respectively); this item accounted for 26% to 43% of the total cost, depending on the country. For Labisa et al., indirect costs represented 21% and 20% of the total cost based on patients' ambulatory status, respectively.

In the study by Schreiber et al., indirect costs were estimated at €21,463 for adult patients and €7,220 for caregivers, totaling €28,683, representing 36% of the estimated total cost (2013 value). In the study by Teoh et al., indirect costs accounted for only 6% of the total cost, but this was related to the valuation method that did not consider changes in working conditions (reduction or cessation of professional activity) related to the patient's illness. However, the surveyed parents reported having reduced their working hours in 29% of cases and completely stopped working in 21%.

Soelaeman et al. studied the productivity loss of mothers of minor patients with Duchenne's disease (n=96) compared to a control panel of mothers of healthy children (ratio 1:4). Indirect costs were valued using the opportunity cost approach. The authors estimated an average salary loss of $8,816 per year, which increased with the child's loss of mobility (-$41 when the child is ambulatory; -$13,828 up to 3 years after loss of mobility; -$23,995 beyond 4 years of mobility loss).

These data demonstrate that the cost of managing Duchenne's disease must consider not only direct medical costs but also non-medical costs, including informal care, and indirect costs, which represent a significant portion from a societal perspective. There is very little information available in France, making this assessment relevant in the context of developing new treatments that could substantially alter the nature of these costs.

In this study, we will thus focus on estimating all relevant expense categories from a societal perspective, considering both minor and adult patients who may have professional activities. The medico-social aspect and the collection of aids and benefits received will also provide insight into the nature of support available for French families.

The project's aim is to meet the expectations of HAS and CEPS by providing medico-economic data for the evaluation of the gene therapy product currently being developed by Pfizer (fordadistrogene movaparvovec - PF-06939926). Clinical development began with a phase 1b (NCT03362502); a phase 3 is currently recruiting for ambulatory patients aged 4 to 7 years (NCT04281485) as well as a phase 2 (NCT05429372) for patients aged ≥2 to <4 years.

2.2 Hypothesis

In addition to the EPARDYS study of direct reimbursed medical costs, the aim of this study will be to carry out a specific analysis that takes into account the other costs associated with the management of the pathology, i.e. the direct costs of the healthcare sphere2 not eligible for reimbursement, the medico-social sphere and the domestic sphere, as well as the indirect costs associated with lost productivity.

2.3 Target population

This study will focus on DMD patients of all ages included in the BNDMR. This national database gathers data on all patients treated in rare disease expert centers accredited by the DGOS, and shows a gross number of 2,028 DMD patients as of March 1, 2022.
A sample of these patients (enabling the composition of the patient/caregiver couples concerned by this study) will be drawn up by stratified randomization. Participant selection criteria are detailed in chapter 5.

2.4 Ratio benefits/risks

This is a descriptive study, the aim of which is to analyze the costs borne by patients and their caregivers, as well as the costs associated with informal help, in the context of DMD management in France. No individual benefit is expected from participation in this study, which will contribute to improving knowledge of the various expenses associated with the disease.
The only constraint for participants will be to complete a questionnaire, which will be sent to them beforehand and then completed during a 30-minute interview with a clinical research associate, in order to gather the information required for the proposed cost analysis.
All in all, the benefit/risk balance for the privacy of patients and families is therefore acceptable.

Table 1: Publications evaluating the costs of Duchenne Muscular Dystrophy, including informal assistance and indirect costs.

Référence	Pays	Nombre de paires patients/aidants	Coût total moyen annuel	Coûts directs		Coûts indirects	
				Non médicaux	Dont aide informelle	Perte de productivité aidants	Perte de productivité patients
Larkindale et al. 2013	USA	N=131	50 952 $	12 939 $	Non	Perte de revenu annuelle = 15 481$	NA
Landfeldt et al. 2014	Allemagne, Italie, Royaume-Uni, USA	N=770	Entre 42 140 $ (Italie) et 75 820 $ (USA)	Entre 17 750 $ (Italie) et 41 110 $ (Royaume-Uni)	Entre 13 160 $ (Italie) et 18 530 $ (Allemagne)	Entre 18 220 $ (Italie) et 21 550 $ (USA)	NA
Schreiber-Katz et al. 2014	Allemagne	N=248	78 913 €	30 884 €	21 279 €	7 220 €	21 463 €
Cavazza et al. 2016	Bulgarie, France, Allemagne, Hongrie, Italie, Espagne, Suède, Royaume-Uni	N=268/154	Entre 7 657 € (Hongrie) et 58 704 € (France)	Entre 6 0 94 € (Bulgarie) et 38 907 € (France)	Entre 5 087 € (Bulgarie) et 33 417 € (France)	NA	295 € (Italie) 495 € (Espagne) 956 € (Bulgarie)*
Teoh et al. 2016	Australie	N=104	46 669 $A	33 557 $A	4 151 $A	3 066 $A	NA
Flores et al. 2020	Espagne	N=36	NA	Non valorisés	Non valorisés	Non valorisés	NA
Soelaeman et al. 2021	USA	N=96	NA	NA	NA	Perte de revenu annuelle = 8 816 $	NA
Labisa et al. 2022	Portugal	N=46	Patients ambulatoires = 48 991 € Patients non ambulatoires = 19 993 €	Patients ambulatoires = 11 890 € Patients non ambulatoires = 29 717 €	Patients ambulatoires = 9 996 € Patients non ambulatoires = 20 772 €	Patients ambulatoires = 4 395 € Patients non ambulatoires = 10 211 €	NA

NA = Non applicable

* Seuls pays pour lesquels une valorisation a pu être réalisée

2.5 Expected benefits

The data controller is a public entity of the AP-HP in collaboration with the national heads of the neuromuscular disease reference centers. The aim of the study is to identify patients' healthcare consumption, document their healthcare expenditure: non-reimbursable expenses, medico-social expenses and loss of productivity, and inform the medical community, associations and authorities about the factors that explain the healthcare expenditure borne by patients and carers.

The expectations for this project are as follows:

- for patients and their carers: understand the consumption of patients and carers in relation to the disease, identify the most significant expenditure items, contribute to the development of the HAS ALD guides.
- for the HAS and Comité Economique des Produits de Santé (CEPS): identify and quantify expenses associated with the disease in the absence of specific treatment.

The aim of the project is to meet the expectations of HAS and CEPS by providing medico-economic data for the evaluation of the gene therapy product currently under development.

Knowledge of disease-related consumption (excluding direct medical costs) as a function of patient characteristics will complement the collection of direct medical costs in the EPARDYS study. It will thus provide a complete picture of Duchenne-related expenses borne by patients and caregivers.

3 OBJECTIVES

3.1 Main objective

Describe the consumption of resources linked to the care of DMD patients other than those eligible for reimbursement, i.e. in terms of: direct medical costs not eligible for reimbursement and medico-social costs, direct non-medical costs and indirect costs.

3.2 Secondary objectives

- Estimate the different types of costs identified for pathology management;
- Estimate costs as a function of disease severity;
- Describe the cost drivers identified.

4 RESEARCH DESIGN

4.1 Study type

This is a national, cross-sectional, non-comparative, sample-based cost analysis survey.

Insofar as this study does not study the pathology itself, nor intervene in its management, it corresponds to research not involving the human person.

4.2 Assessment criteria

4.2.1 Main citerion

Average annualized cost per patient/family.
Table 2 below shows the typology of all the costs considered in this study.

Table 2: typology of all study costs.

		Postes de coûts recueillis dans le cadre de l'étude 'CouDuMyo'
Coûts directs	Coûts médicaux non remboursables	▪ Médicaments en vente libre ▪ Autres produits de santé en vente libre (ex : petits dispositifs médicaux, compléments nutritionnels oraux…) ▪ Equipements techniques de compensation du handicap ▪ Consultations de professionnels paramédicaux non pris en charge par l'Assurance Maladie (ex : ergothérapeute ou psychologue en ville…)
	Coûts liés à la sphère médico-sociale	▪ Auxiliaire de vie, éducateurs spécialisés, assistants sociaux, accompagnement à la scolarité ▪ Hébergement en établissement médico-social ▪ Consultations dans des services médico-sociaux
	Coûts non-médicaux	▪ Adaptation du domicile, adaptation du véhicule ▪ Transports non médicaux ▪ Aide informelle pour les soins (aidant familial, bénévole, autre) ▪ Aide informelle pour les activités quotidiennes ▪ Recours à une aide hors secteur sanitaire pour les actes de la vie quotidienne (ménagère, auxiliaire de vie, etc.)
Coûts indirects	Coûts indirects pour le patient	▪ Pertes de productivité (adulte) ▪ Perte de jours d'école (enfant)
	Coûts indirects pour les aidants	Pertes de temps dédié : ▪ à une activité professionnelle (aidant travaillant), ▪ ou de loisir (aidant non travaillant), hors temps consacré aux soins[2].
Aides financières	Coûts liés aux allocations/aides financières	Dispositifs permettant de financer (hors budget de l'Assurance Maladie dans le cadre de l'ALD) tout ou partie des coûts identifiés (ex : allocation compensatrice pour personne tierce (ACTP), allocation adultes handicapés (AAH), allocation d'éducation de l'enfant handicapé (AEEH), prestations de compensation du handicap (PCH)…)

4.2.2 Secondary criteria

- Average annualized cost by type of cost and by patient/family ;
- Average annualized cost per patient/family for each stage of disease severity;
- Cost drivers identified.

[2] Pour ne pas comptabiliser double avec le coût des soins médicaux

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

- Patients of any age with DMD diagnosed more than 6 months ago;
- Patients included in the BNDMR (ORPHA code: 98896), who do not object to the collection of their data (see BNDMR 'Agreement to be contacted for a protocol') and who are alive at the time they are asked to participate in the study.

Identified patients are those present in the BNDMR with an up-to-date address at their follow-up center.

5.2 Non inclusion criteria

- Patient participating in an interventional clinical study with modification of usual management (see BNDMR 'Patient participating in a protocol');
- Patient and/or primary caregiver objecting to the use of his/her data;
- Patient and/or primary caregiver whose understanding of the French language does not allow them to complete the questionnaire.

5.3 Patients identification in BNDMR

The CO BNDMR will provide the URC ECO with a secure file listing eligible patients identified by a specific identifier (ID_étude), as well as the variables of interest for sampling and the rare disease site considered.

The patient identification period runs from the start date of inclusions in the BNDMR (2017) to January 1, 2023.

5.4 Recruitment methods and feasibility

A random sample of patients will be drawn upon receipt of the CO BNDMR file by the URC ECO. The URC ECO will contact the sampled centers to inform them of the study project, the number of eligible patients in their center and their study ID, and will provide them with the associated documents (protocol, information letter to be given to the patient). Follow-up centers will be able to return to CO BNDMR to obtain the BaMaRa ID of sampled patients, in order to retrieve their contact in the application. Once they have been properly identified by the center, patients and/or their primary caregivers will be contacted by the CRA of their follow-up center, via an information letter explaining the purpose and modalities of the study. The questionnaire will be sent to them in the same letter, so that they can familiarize themselves with it and to give them time to gather the necessary information (expenses, etc.). The main caregiver will then be identified during the call following this letter.

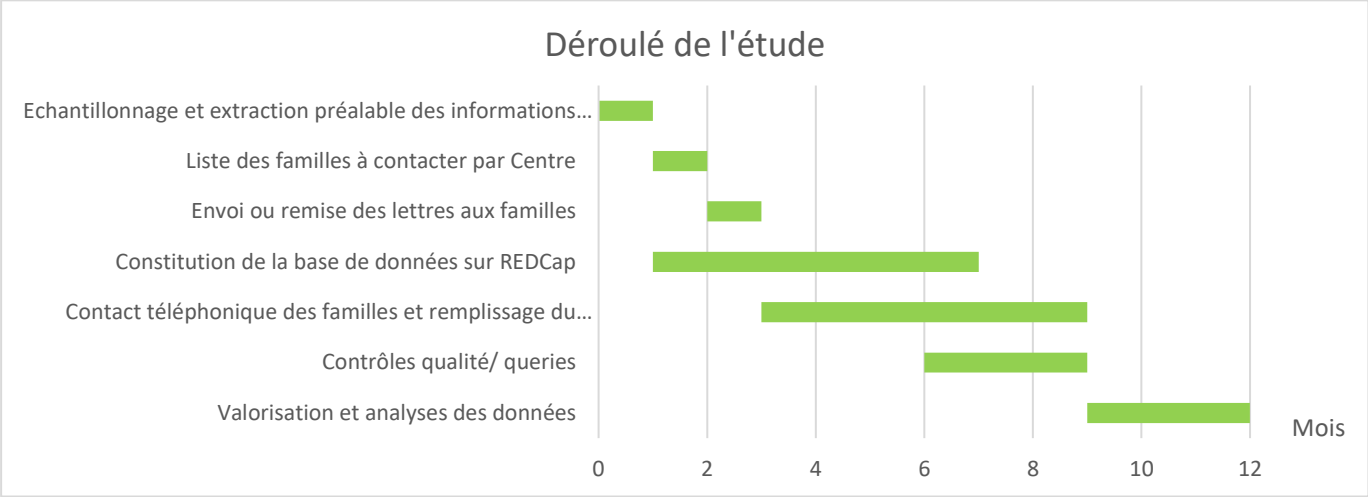
With the BNDMR reporting a preliminary enrolment of around 2,028 DMD patients as of March 1, 2022 [9], the feasibility of the number of subjects required for this study will be ensured.

6 GENERALE ORGANISATION

6.1 Study calendar

Inclusion period: 6 months (01/2024 - 06/2024)
Duration of participation for each patient/caregiver: completion of questionnaire (60 minutes max)
Total study duration: 6 months (01/2024 - 06/2024)
Anticipated start of inclusion: 01/2024

6.2 Schematic diagram



6.3 ***Conduct of the study***

6.3.1 *Inclusion*

Patients likely to participate in the study will be identified following the sampling procedure. Each patient/caregiver pair will first be contacted and informed by letter of the existence of the survey. Any explanations required for a proper understanding of the study will be given to the patient and/or his or her main carer in an information letter explaining the objectives and progress of the protocol.

If the patient and his/her primary caregiver do not object to their participation in the study within 30 days of receiving the information letter, they will be considered as included in the study.

6.3.2 *Questionnaire answering*

The questions are taken from published questionnaires, and a validation of the questionnaire's comprehensibility and acceptability will be carried out on at least 2 child/caregiver and 2 adult/caregiver patients before the information letters are sent out [10].

The standardized questionnaire (see appendix) will be sent to patient/caregiver pairs with the information letter. This will enable participants to gather the information they need to answer the questionnaire.
A clinical research associate from the center which usually cares for the DMD patient or, failing that, from the URC Eco, will then contact the patient and/or his/her main carer by telephone. The interview, lasting a maximum of half an hour, will be based on the questionnaire and will ensure that the participant has understood the questions and that all the required data have been collected.
Variables intended to ensure representativeness or to enable sample adjustment will be collected at inclusion, including commune of residence (used only for adjustment), as well as:
- Patient characteristics: gender, month and year of birth, ambulatory or non-ambulatory status;
- Characteristics of the main caregiver: age, sex, relationship to the patient (degree of kinship, partner or other non-family relationship), family structure (couple, characteristics of other children, etc.).

Variables for cost analysis will also be collected (see chapter 7 + appended questionnaire).

6.4 ***Temporary or permanent shutdown rules***

Subjects may object to their participation and ask to leave the study during the interview, for whatever reason. In the event of premature exit (questionnaire not fully completed), and if the subject does not object, the data collected up to the point of objection will be analyzed.

7 COST EVALUATION

7.1 Perspective

The societal perspective (integrating amounts financed beyond the perspective of compulsory health insurance, i.e. patient out-of-pocket expenses, non-reimbursed costs and lost productivity) will be retained.

7.2 Timeframe

The time horizon will be one year (retrospective) of patient care.

7.3 Identification et quantification des ressources consommées

The resources consumed will be identified and quantified:

1. **Non-reimbursable health resources**

   - Name and weekly quantity of OTC drugs consumed in a representative month;
   - Name, type and quantity of other OTC products (e.g. small medical devices, oral nutritional supplements, etc.) purchased in a representative month;
   - Number and type of paramedical consultations carried out in a representative month;
   - Number and type of non-reimbursable technical equipment for disability compensation purchased since DMD diagnosis.

2. **Ressources de la sphère médico-sociale**

Medico-social costs include those incurred by the medico-social sector. This includes social and medico-social establishments and services (ESMS) and social action assistance.
There are two main types of establishment:

   - Establishments and services for disabled adults;
   - Establishments and services for disabled children and adolescents.

The following variables will be collected:

   - Frequency, duration and type of stay in a social and medico-social institution in the last month;
   - Number of visits to a medical-social service in the last month.

3. **Support for schooling and Professional life**

   - Schooling programs;
   - Socio-professional support services.

The following variables will be collected:

   - Number and type of support staff (carers, special educators, social workers, etc.) in the last month;
   - Type of schooling, specific assistance and how many hours, if not in which structure, and what additional costs in the last month;
   - Working hours, support arrangements and how many hours over the past month.

4. **Other non-medical resources**

   - Recours à une aide hors secteur sanitaire pour les actes de la vie quotidienne (ménagère, auxiliaire de vie, etc.), type et nombre d'heures hebdomadaires ;
   - Aménagements réalisés au domicile, depuis le diagnostic ;
   - Adaptation du(des) véhicule(s) et/ou acquisition d'un véhicule aménagé, depuis le diagnostic
   - Modalité des transports non médicaux, fréquence et kilométrage hebdomadaire.

5. **Informal help**

- Number of caregivers over 18 years old in total, degree of kinship;
- Number of hours spent with the patient providing support for care, daily living activities, and instrumental activities of daily living.

6. Productivity loss

- For the primary caregiver: Changes in situation, absenteeism, and presenteeism related to DMD;
- For the patient: Absenteeism and presenteeism (school or work) related to DMD.

7. Help and allocations

The allowances include disability compensation (PCH), compensatory allowance for a third party (ACTP), child disability education allowance (AEEH) and its supplements, adult disability allowance (AAH), and the increase for independent living (MVA).
The following variables will be collected:

- Allowances received, type, and total amount;
- Destination (compensation for non-medical costs, loss of productivity, etc.): not requested in the questionnaire; this item will be subject to a post hoc analysis

7.4 Resource valorization

Direct medical and non-medical costs will be annualized, assuming consistent/representative resource use over the measurement period (months).

1. Non-reimbursable healthcare resources

- Weekly quantity valued at the average sale price;
- Quantity of other over-the-counter products (e.g., medical devices, oral nutritional supplements (ONS), etc.) valued at the average sale price;
- Number of hours of paramedical care valued at the corresponding wage/convention rate (if available);
- Quantity of technical equipment for disability compensation valued at the average sale price.

2. Medico-social resources

- Use of medico-social support: number of hours valued at the service rate, or, if unavailable, at the average hourly wage of equivalent professionals in France;
- Total costs of stays and consultations in medico-social facilities related to the specified medical condition within the medico-social sector.

3. Other non-medical resources

- Home adaptations: family expenses (lifetime);
- Modification of vehicles and/or purchase of an adapted vehicle: family expenses (lifetime);
- Non-medical transportation: weekly mileage valued according to the mileage reimbursement rate for personal vehicles.

4. Informal help

Care hours provided by caregivers valued at the cost of a replacement salary, according to the Proxy Good Method (PGM), and hours for activities of daily living valued at the average salary of a housekeeper.

5. Productivity loss

Lost work hours related to the DMD (Degenerative Motor Disorder) that do not pertain to caregiving, valued at the average hourly wage in France.

6. Assistance and allocations

Total monthly benefits related to DMD (Degenerative Motor Disorder) received by the patient and/or the family in the medico-social sphere.

8 STATISTICAL ASPECTS

8.1 Number of necessary subjects

The study published on the costs of DMD in Portugal [1] was based on a sample of 46 patient/caregiver pairs without justification for the sample size. The international study collected data from 100-200 patients per country [6]. In France, as of March 1, 2022, the BMDMR (National Registry of Patients with Rare Diseases) reported 2,028 DMD patients. While it is not possible to rely on the French cost data collected by Cavazza et al. 2016, which is based on only two patients [4], we can examine other countries where the values are not aberrant and where there is generally a coefficient of variability (sd/m) of 1. The sample size for a precision of 15% is thus 171 patient/caregiver pairs according to the recommendations of Johnston et al. 2019 [11]. The chosen method of telephone interviews assumes that there will be no non-responses, and since this is a cross-sectional study without randomization, interviews will continue until this number is reached. Stratification in terms of sex, age, and location will be performed, and then families will be randomly selected within each stratum to obtain a representative sample of the BNDMR population. The a priori number of strata is 16 (2 (sex) x 4 (age groups) x 2 (annual follow-up at center vs. no regular follow-up)).

8.2 Population

All the participants surveyed will constitute the analysis population.

8.3 Statistical methods

Cost data will be described in terms of means, variances, and confidence intervals. The normality or non-normality of the cost distributions will be checked. Costs (direct and indirect) will be described among patients living as of December 31, 2023. Analyses will also be conducted by level of mobility.

8.4 Method for Handling Missing Data

It is not planned to compare non-respondents with respondents but to solicit new patient/caregiver pairs while maintaining representativeness with respect to the BNDMR population. The number of missing data will be limited by constructing short and explicit questionnaires and through the direct interview method conducted by a clinical research associate. In the case of missing data during the completion of the survey, or if the interview is interrupted, follow-ups may be organized if the family has given their consent.

8.5 Exclusion of Data in Statistical Analysis. Management of Changes Made to the Analysis Plan

A detailed statistical analysis plan will be drafted before the database is frozen. It will take into account any modifications to the protocol or any unexpected events that occur during the study and impact the analyses presented above. Planned analyses may be supplemented in accordance with the study objectives. Any subsequent changes to the statistical analysis plan must be justified and will result in a new version of the document. These deviations from the analysis plan will be reported in the final study report. All documents will be kept in the study file.

8.6 Person Responsible for the Analyses

Data analysis will be conducted by a statistician from the URC Eco under the supervision of Professor Durand-Zaleski.

9 RIGHTS OF ACCESS TO DATA AND SOURCE DOCUMENTS

9.1 Collected Data

In the first phase (Phase 1), the sampling variables will be communicated by the BNDMR (study pseudonym, age, sex, place of residence, care site, age at diagnosis). In the second phase (Phase 2), the data necessary for this study will be collected through questionnaires directly from the participants and will be entered by a clinical research associate into an electronic data collection notebook (eCRF) developed using the CleanWeb™ solution (Telemedicine Technologies).

As this is a cross-sectional study, the interview serves as inclusion. A participant who refuses the interview will therefore not be considered included. Participants may request to withdraw from the study during the interview, and the questionnaire will then be incomplete: if the subject does not oppose it, the data collected up to that point will be retained and analyzed.

9.2 Source Documents

Source documents are defined as any original document or object that proves the existence or accuracy of a data point or fact recorded during the clinical study. This will include the questionnaires completed by the patient/caregiver pairs included in the study. They will be kept for the duration of the study and until the completion of data analysis, and then archived for 5 years from the date of questionnaire completion.

9.3 Data Confidentiality

Individuals with direct access to the data will take all necessary precautions to ensure the confidentiality of information related to participants, particularly regarding their identity and the results obtained.

These individuals, like the investigators themselves, are subject to professional secrecy (as defined by Articles 226-13 and 226-14 of the Penal Code). During the research, the data collected on participants and transmitted to the sponsor by the investigators (or any other specialized participants) will be coded.

Under no circumstances should the names of the individuals concerned or their addresses be clearly displayed. Only the first letter of the subject's last name and the first letter of their first name will be recorded, accompanied by a coded number specific to the study indicating the order of inclusion of the subjects.

10 CONTROL AND QUALITY ASSURANCE

10.1 Qualification of Participants

The coordinating investigator, the qualified person, or the scientific officer ensures that the research participants are qualified for the tasks assigned to them.

10.2 Data Quality

A review of the data at the end of the interview by the Clinical Research Associate (CRA) and the patient will allow for checking their consistency and ensuring that no omissions have occurred. A data management plan will be established to determine consistency checks. Descriptive analyses will be conducted on available data, assuming that missing data are non-informative, and the counts of missing values will be described for each variable, if applicable.

11 ETHICAL CONSIDERATIONS

11.1 Role of the Sponsor

The Assistance Publique - Hôpitaux de Paris is the sponsor of this research, and by delegation, the Delegation for Clinical Research and Innovation (DRCI) carries out its missions in accordance with Article L.1121-1 of the Public Health Code. The Assistance Publique - Hôpitaux de Paris reserves the right to interrupt the research at any time for administrative reasons.

11.2 Information for Subjects and Right to Withdraw

In accordance with Article L1121-1-1 of the Public Health Code, no non-interventional research may be conducted on a person who has opposed it after being provided with the information required by Article L1122-1 of the same code. Patients and their caregivers will be fully and fairly informed, in terms understandable to the general public, about the objectives, their rights to oppose their participation in the study, and the possibility of withdrawing at any time. All this information is included in an information form provided to the patient and their caregiver.

12 DATA MANGEMENT AND CONSERVATION

12.1 Observation Notebook

The observation notebook will only include the data necessary for analysis for publication. Other patient-related data necessary for follow-up outside the study will be compiled in their medical file. An electronic observation notebook (eCRF) will be used for data collection.

12.2 12.2 Data Management

The responsibility for processing the project is ensured by AP-HP (Direction des Services Numériques (DSN) for Phase 1 and Direction de la Recherche Clinique et de l'Innovation (DRCI) for Phase 2). The project team within the DSN is represented by the following members of the BNDMR operational unit:

- Dr. Anne-Sophie JANNOT, Medical Director
- Nabila ELAROUCI, Chief Data Officer
- Bénédicte SABIN, Project Manager

The party responsible for implementing the processing is the Direction de la Recherche Clinique et de l'Innovation (DRCI) within AP-HP, represented by Professor Isabelle Durand-Zaleski. The Data Protection Officer (DPO) is Ms. Donatienne Blin, within the DSI of AP-HP, 33 bld Picpus 75012 PARIS, email: donatienne.blin@aphp.fr, phone: 0683988971.

The data collected from the questionnaires administered to patients will not be matched with the BNDMR data; the two databases will remain distinct from the beginning to the end of the study.

A data collection notebook will be created under CleanWeb™ for entering data from the questionnaires administered to patients. CleanWeb™ is a secure, controlled web-access solution for creating structured forms (eCRF) for manual information entry (Electronic Data Capture - EDC); this solution, complementary to EDS, is used by AP-HP for electronic management of clinical studies. The eCRF will be developed under the responsibility of a data manager. Only authorized individuals may access the eCRF through a secure login (username and password).

The data collected will be entered by a CRA into the eCRF at the time of the interview. The eCRF will be pseudonymized with a number for each family. Only the CRA at each center will have access to the name and phone number required for the interview, as well as the number corresponding to each family. The correspondence table for the center, populated during the data collection period, will be deleted as soon as the database is frozen.

These data will be retained for the duration of the study and until the end of data analysis. In accordance with MR004 from CNIL, data must be retained for a maximum of 2 years after the last publication or until the final report is signed before archiving, according to the regulations in force.

12.3 Regulatory Compliance with GDPR

This study falls within the scope of the "Reference Methodology" (MR004) in application of the provisions of Article 54, paragraph 5 of Law No. 78-17 of January 6, 1978, as amended, relating to data processing, files, and freedoms. This amendment was approved by decision on January 5, 2006, and modified on July 21, 2016. This study will be registered in the public catalog of studies within the HDH and on the AP-HP registry. Finally, a PIA will be conducted before implementation.

12.4 Archiving

The following documents will be archived under the study name under the responsibility of the coordinating investigator and associated investigators at each center for 15 years:

- Protocol and appendices, any amendments,
- Individual data (authenticated copies of raw data),
- Monitoring documents and correspondence related to the research.

The sponsor is also responsible for organizing the retention of statistical analyses and the final study report during the regulatory archiving period. No transfer or destruction may be carried out without the sponsor's agreement. At the end of the 15 years, the sponsor will be consulted regarding destruction. All data, documents, and reports may be subject to audit or inspection.

13 PUBLICATION RULES

Scientific communications and reports corresponding to this study will be prepared under the responsibility of the principal investigator of the study with the agreement of the associated investigators. Patients and families will be informed of the results via the BMDMR website. The co-authors of the report and publications will include the investigators and clinicians involved, in proportion to their contribution to the study, as well as the biostatistician and associated researchers.

The publication rules will follow international recommendations (N Engl J Med, 1997; 336:309-315). The study will be registered in a publicly accessible clinical trial registry (clinicaltrials.gov) before the inclusion of the first patient.

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