# Understanding Complex Care Situations of Neuromuscular Diseases:
# Patient-Reported Measures, Cost-of-Illness and Status Quo of Telemedicine

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## Abstract

Understanding the actual care situations and outcomes in the everyday lives of patients is the pivotal focus of health services research (HSR). Manifold qualitative and quantitative methods are utilised in HSR to research the processes, structures and interventions of health care. Here, the functions of HSR are to describe, elucidate, develop, implement and evaluate the above-mentioned aspects of health care within complex environments. Implementation science (IS) complements the aims of HSR by investigating the uptake of effective interventions into health care. Within these areas, considerable attention has been devoted to the dual complexity of health care, as complex interventions are performed in complex settings. Accordingly, as an example, neuromuscular diseases (NMDs) are classified into more than 850 different complex diseases, of which a majority have a rare nature. NMD patients suffer primarily from chronic progressive disease courses and experience physically various forms of muscle weakness that limit physical functions. Patient-reported outcomes (PROs), like the health-related quality of life (HRQoL), are often decreased in NMD patients. In addition, multidisciplinary disease management or expensive therapies entail substantial cost-of-illness (COI). Nevertheless, effective therapies are lacking for many NMDs. Applying HSR and IS to the example of NMDs, few studies have focused on the exploration or description of patient-reported outcomes and experiences (PREs) within actual complex care situations. In addition, there is scant evidence for the implementation of innovative telemedicine interventions in NMDs which has been proven to optimize outcomes in other diseases. Therefore, this cumulative thesis includes five research papers in the areas of HSR and IS in order to explore, describe, and assess aspects of the actual complex care situations in NMDs, mainly focusing on inclusion body myositis (IBM) and Charcot-Marie-Tooth neuropathies (CMT).

Theoretical as well as empirical studies were undertaken by incorporating mixed methods. Firstly, research paper #1 constitutes a systematic review of the HRQoL, mental health and illnesses in IBM patients. Secondly, the current status quo of the literature described in research paper #1 laid the basis for an in-depth qualitative study in IBM for the investigation of the patient-reported HRQoL and experiences in the course of the patient journey (research paper #2). Thirdly, a quantitative assessment was applied based upon preliminary work in CMT patients to assess the HRQoL and satisfaction with health care (research paper #3). Fourthly, research paper #4 examined the COI in IBM and considered PRO- and PRE measures (PROMs, PREMs) for further analyses. Lastly, research paper #5 provides an overview of the current use

of telemedicine in NMDs and describes the barriers and facilitators for the respective implementation.

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## List of Abbreviations

| | |
|---|---|
| ADL | Activities of daily living |
| CFIR | Consolidated Framework for Implementation Research |
| CMT | Charcot-Marie-Tooth neuropathies |
| COI | Cost-of-illness |
| DM | Dermatomyositis |
| DMD | Duchenne muscular dystrophy |
| eHealth | Electronic health |
| ENMC | European Neuromuscular Centre |
| FSHD | Facioscapulohumeral muscular dystrophy |
| HNPP | Hereditary neuropathy with liability to pressure palsies |
| HRQoL | Health-related quality of life |
| HSR | Health services research |
| IBM | Inclusion body myositis |
| IBMFRS | Inclusion Body Myositis Functional Rating Scale |
| ICT | Information and communication technologies |
| IS | Implementation science |
| IIM | Idiopathic inflammatory myopathies |
| IQTiG | Institute for Quality Assurance and Transparency in Healthcare |
| IQWiG | Institute for Quality and Efficiency in Health Care |
| IVIg | Intravenous immunoglobulin |
| MD | Muscular dystrophies |
| mHealth | Mobile health |
| NMD | Neuromuscular disease |

| | |
|---|---|
| PM | Polymyositis |
| PRE | Patient-reported experience |
| PREM | Patient-reported experience measure |
| PRO | Patient-reported outcome |
| PROM | Patient-reported outcome measure |
| RCT | Randomized controlled trial |
| sIFA | sIBM Physical Functioning Assessment |
| SCQ-D | German version of Self-Administered Comorbidity Questionnaire |
| SMA | Spinal muscular atrophy |
| WHO | World Health Organisation |

# 1. Introduction[1]

The fundamental aim of health services research (HSR) is to gain an understanding of the actual care situation in the *everyday life* of patients.[1, 2] This multidisciplinary research field comprises several branches of science such as medicine, epidemiology, implementation science (IS), health economics, social science and public health.[3] Investigating the uptake of evidence from biomedical and clinical research in routine health care is essential in HSR.[2, 4] In biomedical and clinical research the efficacy of interventions (e.g., treatment options) is derived under controlled conditions as in randomized controlled trials (RCTs), whereby the over- or underestimation of an intervention's impact outside of the respective study setting is likely.[5] RCTs in older adults, for example, frequently lack comprehensive descriptions regarding such individual characteristics such as frailty, mental and physical condition or the respective social environment of interventions to draw clear conclusions about the external validity.[6] By contrast, HSR generates new evidence for the effectiveness, which is defined as the effect under routine conditions.[7, 8] A wide range of qualitative and quantitative methods is used in HSR to elucidate, describe, develop, implement and evaluate interventions as well as structures and processes in the course of the patient journey.[9, 10] The German government has spent more than 115 million Euros on HSR projects within the Innovation Fund between 2016 and 2024.[11] Of the total 362 funded projects until 2022, only seven projects focused on the patient journey and five on developing outcome instruments to assess health-related quality of life (HRQoL), while 28 focussed on the improvement of cost-effective and need-oriented health care.[11]

Besides investigations in the cost, access and quality of health care, *patient-centredness* is further crucial in HSR.[2, 3, 12] In 2000 Mead and Bower already summarised five core dimensions of patient-centredness: "biopsychosocial perspective, 'patient-as-a-person', sharing power and responsibility, therapeutic alliance and 'doctor-as-a-person'"[13]. This also illustrates that patients are increasingly seen as equal decision-makers and advocates in their health care.[14–16] From an international perspective, greater attention has been given to patient-centredness over more than the last two decades.[17–19] Patient-reported outcomes (PROs) and experiences (PREs) are part and parcel of several legislative frameworks regarding

[1] The content of this section is partly taken from the research papers included in this thesis. The citation style of the papers has been used in order to improve the readability.

reimbursement processes and benefit assessments in pharmaceutical therapies and even in digital health applications.[20–22] The Institute of Medicine characterizes the role of patient-centredness as one domain of quality of care as well as of patient-reported measures, in the meaning of instruments to assess patient outcomes and experiences.[23] By definition, it allows to distinguish between the following: perceptions or statements directly from the patients, without external influences, in respect of (1) aspects of the *health status* (outcome; PRO) or (2) aspects of the viewed *health care processes* (experience; PRE).[24, 25] Historically, HSR has also been synonymously with 'outcome research' in regard to patient values, preferences and experiences.[26] In this thesis, PROs and PREs are differentiated and are not summarised as in the aforementioned term of Clancy and Eisenberg (1998). Hence, outcomes comprise the results of health care services (outputs) on a patient level such as HRQoL or pain. Experiences are represented in the form of patient satisfaction, perceptions and appraisals of the experienced health care service delivery.[25]

Within the scope of patient-centred drug development or medical device evaluations in the US, PRO and PRE data are derived from different individual care situations in the course of the patient journey.[27, 28] The term patient journey refers to the entire phase from the patient's point of view that is related to a specific disease or syndrome – starting with the first perception of symptoms or changes in the activities of daily living (ADL) and ending with the completion of therapies or even death. This consideration offers the possibility to research medically and also economically relevant aspects of all health care stakeholders involved in order to optimize the quality of care.[29] Patients and their families are typically not only faced with the physical or psychological consequences of a disease and therefore experience emotional or social challenges in the course of their journey.[30] Over time, patients also experience several points of contact with health care professionals, health insurances, governmental institutions or other service providers, interacting each time within different context factors.[29, 31]

Besides the individual input, output and outcome factors in health care delivery, HSR focusses explicitly on the above mentioned context factors of health care provision and the associated changes of processes or services, named as throughput.[2] Pfaff and Schrappe initially defined their Throughput Model in 2003 and redefined this in 2016 to also include the feedback of output and outcome on the input as well as the respective influence on the throughput.[1, 32] Interventions, context factors and the actual health care provision together constitute a

complex system, whereby a “double complexity” [33, 34] ensues: firstly, the complex context and secondly, complex interventions.[2] On a higher level, complex interventions are, for example, characterized by a multitude of various outcomes, behaviour patterns of the involved persons, and target groups, as well as interacting components.[35] When describing, explaining, implementing or evaluating complex interventions within a complex context in routine practice, the methods and frameworks of IS could be useful to complement HSR. IS scientifically investigates the uptake of evidence into health care, whereby effective interventions and implementation strategies are central to improving the quality of care.[36] Previous research has generated numerous diagnostical frameworks, which compile factors that influence the implementation of interventions.[37–40] Damschroder et al. are a good example of the efforts for establishing frameworks in IS, as they defined the Consolidated Framework for Implementation Research (CFIR). The CFIR summarises the following five constructs to structure barriers and enablers of an implementation: characteristics of the intervention and the individuals, outer and inner setting and lastly the implementation process itself.[41, 42] In 2022 an updated version was published, even including an addendum to better distinguish between innovation and implementation outcomes.[43, 44]

It can be inferred that HSR and IS complement each other and create synergies to improve the quality of care and patient outcomes. As both consider the various levels of complexity in health care, complex diseases and complex care situations prove to be predestined research fields when combining HSR and IS. The terms complex disease or complex disorder are mostly used as an umbrella term to describe conditions that are multifactorial and determined by mutations of a rare nature and occurring in heterogenous genes.[45, 46] Neuromuscular diseases (NMDs) are often attributed to complex diseases, but they are also associated with complex care situations. Multidisciplinary health care professionals are involved during the patient journey to support the patients with their chronic and mostly progressive NMD.[47–51] Over the last few years, improved treatment options and significant achievements in genetics have established and enhanced, but also changed our understanding of these mostly rare diseases.[52, 53] The complexity of the different treatments in NMDs can be illustrated by comparing spinal muscular atrophy (SMA) with inclusion body myositis (IBM). To date, breakthrough innovations in gene therapy make three effective therapeutic options available for SMA patients.[54] The cost for this pharmacotherapy range between US $340,000 per year for Risdiplam (Evrysdi) and up to US $2.15 million for a single dose of Onasemnogen-Abeparvovec

(Zolgensma®).[54] IBM is until now refractory to treatment. Besides treatment attempts with intravenous immunoglobulins (IVIg), only supportive approaches are recommended in the long term.[49] NMDs differ not only in their therapeutic options, but also in their overall disease burden as well as in their prevalence rates, ranging from 0.1 up to 60 per 100,000.[55–57] Moreover, the scarce evidence for the economic burden in rare diseases in general also applies to NMDs.[58, 59] In the US, the medical costs in NMDs were inherently estimated to be US $46 billion per year. Nevertheless, comprehensive national cost-of-illness (COI) estimations for all NMDs together are lacking from an international perspective and also the data for Germany are rather published for individual NMDs, like Charcot-Marie-Tooth neuropathies (CMT), SMA, myasthenia gravis or facioscapulohumeral muscular dystrophy (FSHD).[60–62] The annual societal per capita cost in NMDs show varying distributions of the costs, which in turn justifies the need for individualised COI studies.[61–66] In addition, the various forms of muscle weakness as the primary symptom in most NMDs cause enormous changes in the everyday life of patients and their families.[67] Therefore, patient registries have an auspicious potential for HSR by collecting valuable data about the patients, not only to draw conclusions about their actual medical condition, but also about their actual care situations and the implications of innovative therapies.[68–70] Besides the remarkable evolution of pharmacotherapy and gene therapy in NMDs, telemedicine could also play a relevant role in the future health care of NMDs by generating innovative efficiency potentials. Based on study results during the COVID-19 pandemic, it could be concluded that there is still an enormous potential for optimisations in the management of chronic diseases in consideration of the various information and communication technologies (ICT).[71, 72]

A key issue for the previously mentioned distinctions in NMDs is the need for specific treatment plans and a subtle understanding of the respective complex care situations in order to eliminate ethical problems, provide the best available medical and non-medical support, allocate finite health care resources, and finally optimize patient outcomes. The remarks presented provide the scientific and practical context for this cumulative doctoral thesis. Five research papers are embedded into HSR and IS in complex care situations of NMDs. To obtain information from different perspectives, a mixed methods approach was applied: firstly, to obtain information from two selected NMDs (IBM and CMT) about relevant PROs, PREs and COI; secondly, to obtain information from all NMDs about the status quo of telemedicine. As HSR and IS aim to provide aids for real-life decision making, the results of this thesis are

relevant for a great many stakeholders: from health politics to medical industry, payers as well as professional and informal health care providers. Further important addressees of this research papers are the affected patients and families confronted daily with these grave diseases.

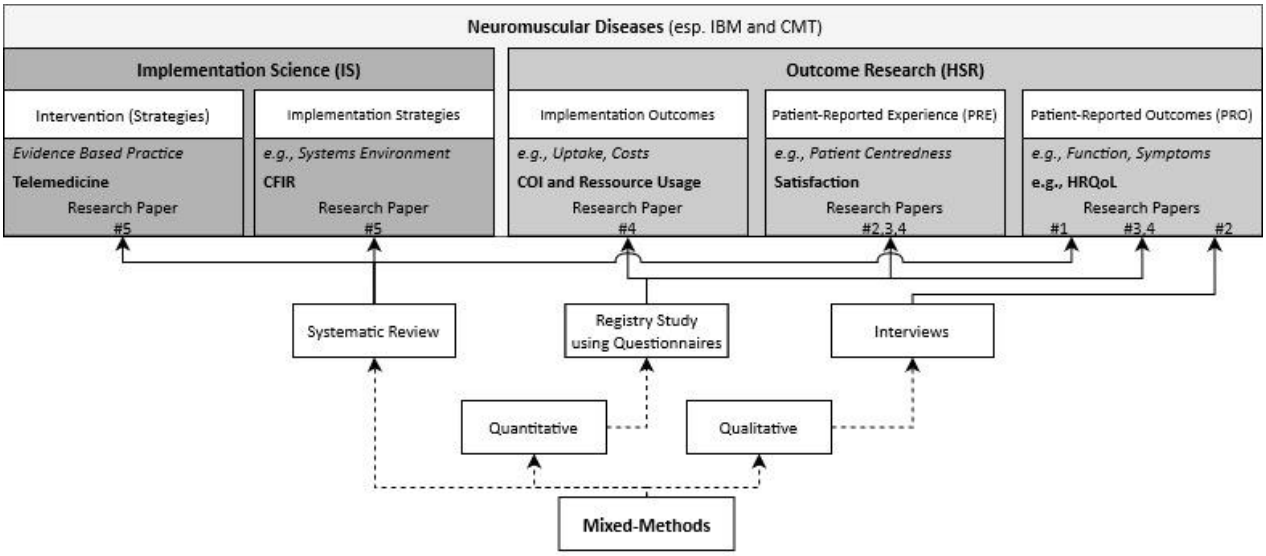


***Figure 1:*** *Health care services research and implementation science in complex care situations of neuromuscular diseases: selected research foci and methods. Author's presentation based on Proctor et al. (2009)* [73] *and Chorwe-Sungani et al. (2021)* [74]*.*

Figure 1 depicts the research foci and the applied methods of the research papers, as well as the embedding in the research fields of HSR and IS. Theoretical frameworks and models of IS, HSR and psychology structure the empirical and literature-based findings of the five research papers and are described in more detail from Section 2 onwards. The following sections of this cumulative thesis are structured according to the main topics outlined: complex care situations of NMDs (Section 2.1), patient-reported outcome and experience measures (PROMs; PREMs) in HSR (Section 2.2) and determinants of implementation (Section 2.3). Firstly, to contextualise and characterise IBM and CMT within the broad spectrum of NMDs, the most relevant commonalities and differences between these two selected diseases are described in Section 2.1. The comparison of the medical characteristics allows one to lay the foundation for a deeper understanding of the needs and demands of the respective complex health care and illustrates insights into current research in IBM, CMT and NMDs in general. Until now, few studies have undertaken in-depth investigations to explore and describe patient-relevant outcomes and the care situation in IBM and CMT. Research papers #1,2 and 4 focus on IBM, whereas research paper #3 considers CMT in the context of outcome research and HSR,

respectively. Research paper #5 covers the field of IS and comprises the entire NMD spectrum as population under investigation in order to point out the existing status quo of telemedicine usage and determinants of practice.

Secondly, Section 2.2 provides the background of descriptive HSR in this thesis by including principles of participatory health care research. The selection of patient-relevant outcomes and their assessment instruments in IBM and CMT are elucidated. Precise literature searches and the related evaluation of the existing evidence of PROs and PREs in the selected populations are the sine qua non for further profound empirical studies. A systematic review (research paper #1) provides an overview of major factors suggested to determine and influence HRQoL as well as mental health and mental illnesses in IBM patients. Previously applied PROMs on the HRQoL and mental health in IBM were extracted and the HRQoL characteristics were categorised in the physical, psychological and social HRQoL dimensions. In addition to the preliminary literature review, with the inclusion of qualitative and quantitative evidence, research papers #3 and #4 apply empirical quantitative methods and research paper #2 empirical qualitative methods. In every research paper the use of patient-reported data was essential in order to ensure a high patient-centredness. The registry study in IBM (research paper #4) details the resource utilisation and estimated health care cost from the patient's point of view, whereby PRO and PRE data are used for further analysis. Moreover, PRO and PRE data were collected and analysed in a registry study in CMT (research paper #3). A descriptive and explorative approach in research paper #2 is used to complement the literature review (research paper #1) and gain an in-depth understanding of the actual care situation and HRQoL in IBM as a pre-study for research paper #4. It is important to mention that the aforementioned empirical studies were conducted in the German health care system.

Thirdly, a taxonomy of telemedicine and an implementation framework of IS was used in this thesis to provide a structured overview of existing telemedicine interventions in NMDs. Section 2.3 provides the context for the second systematic review (research paper #5), which applies a broader international view in NMDs, not limited to the German health care system.

Thus, Section 3 summarises the results obtained (Section 3.1) and gives perspectives for future HSR and IS in NMDs, as well as key suggestions for future research (Section 3.2). The references in this cumulative thesis are indicated in Section 4. Finally, the appendix (Section 5) presents an index of all research papers (Section I), a declaration of the author's contributions

to the research papers (Section II), and lastly the respective extended abstracts of the research papers (Sections III–VII).

# 2. Overview and Context of the Research Papers[2]

## 2.1 Complex Care Situations of Neuromuscular Diseases

An understanding of the relevant medical background under investigation is vital in HSR and IS to interpret study results and suggest recommendations for clinical practice. Section 2.1 comprises an overview of disease characteristics, as well as the most common diagnostics, treatment and care approaches in NMDs in general, and in IBM and CMT in particular.

The umbrella term NMDs encompasses more than 850 various diseases, which together form this heterogenous disease group.[59, 75] NMD patients experience common symptoms like muscle weakness, torpidity or cramps, although symptoms vary within the specific diseases.[76] Besides muscle loss and weakness, cardiac involvement as well as dyspnoea and dysphagia often lead to fatal disabilities and limitations in ADL.[67, 77, 78] NDMs are of a rare nature and are mostly inherited and seldom acquired during the patient's life (e.g., myositis).[79] Therefore, the patient journeys differ regarding the disease awareness, but also regarding the presence of a timely and definite diagnosis, which is the indispensable starting point for adequate treatments.[80] In addition to the brief introduction to NMDs in Section 1, an overview of the disease classification in NMDs is decisive to contextualise the selected patient populations in this thesis. The complexity of disease classification in NMDs is increasing due to substantial progress regarding the detection and allocation of affected genes (currently more than 500 genes).[75] The phenomena of phenotypic divergence (one gene can cause several diseases) and phenotypic convergence (with one disease due to several genes, e.g., CMT) requires continuously updated online databases for the respective dynamic and increasing knowledge management in NMDs.[81] For the purpose of this thesis, a classification that differentiates between seven major categories of NMDs is reasonable (Figure 2) [82, 83]: muscular dystrophies (MD), myopathies different from dystrophies, motor neuron diseases, mitochondrial diseases, peripheral nerve diseases, neuromuscular junction diseases and ion channel diseases.

The two specific NMDs under investigation in this thesis are predominantly IBM (research papers #1,2,4) and CMT (research paper #3). IBM belongs to the group of myopathies (Figure 2), more precisely to inflammatory myopathies or myositis, respectively.[82, 84] Within this

[2] The content of this section is partly taken from the research papers included in this thesis. The citation style of the papers has been used in order to improve the readability.

disorder family five different specific diseases are grouped in turn as idiopathic inflammatory myopathies (IIM), namely polymyositis (PM), dermatomyositis (DM), immune-mediated necrotising myopathy, overlap myositis and IBM.[85] Besides this sporadic muscle disease IBM, formerly often also abbreviated as sIBM, a distinction has to be made regarding the hereditary inclusion body myopathy. Although both diseases (IBM and hereditary IBM) share some pathological features, hereditary IBM is a distinct disease showing different patient characteristics, disease course and clinical phenotypes.[86–88] To clarify this, this thesis exclusively refers to patients with an acquired IBM and not with hereditary IBM. Turning to peripheral nerve diseases, these include CMT (Figure 2), which could further be differentiated into demyelinating (CMT1) and axonal (CMT2) forms, together also hereditary motor and sensory neuropathy HMSN, as well as into intermediate forms (distal hereditary motor neuropathy; hereditary neuropathy with liability to pressure palsies, HNPP; hereditary sensory (and autonomic) neuropathies).[89–92] However, the literature describes broad phenotypic overlaps with various neurological disorders (e.g., hereditary sensory and autonomic neuropathies, distal hereditary motor neuropathies, SMA and hereditary spastic paraplegia), what complicates exact comparisons between studies. Within this cumulative thesis, the investigated study population in research paper #3 is referred to as CMT patients, though there were also some patients included with such phenotypic overlaps (e.g., HNPP).

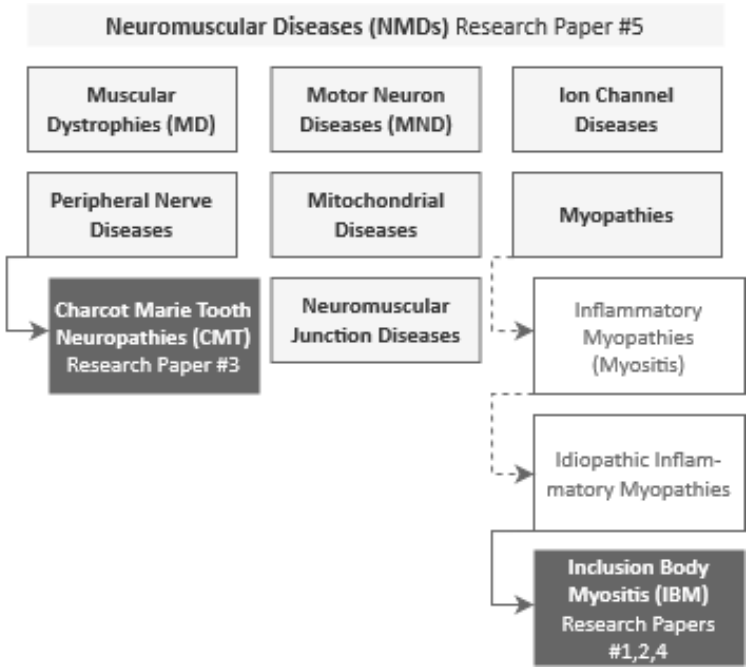


***Figure 2:*** *Classification of neuromuscular diseases with focus on investigated study populations with reference to the research papers. Author's presentation based on Cantó-Santos, Grau-Junyent, Garrabou (2020)* [82].

At this point it is useful to illustrate the clinical relevance of NMDs in general, IBM and CMT. There are considerable uncertainties and research gaps regarding the actual **prevalence** rates in NMDs and thus the absolute patient numbers. In contrast to the prevalence rate of all NMDs in general (cf. Section 1, range of 0.1 up to 60 per 100,000) [55], CMT was estimated to be prevalent in 1 per 2,500 (41 per 100,000) [89, 93]. A recently published meta-analysis from 2023 identified pooled prevalence rates of 17.69 per 100,000 in CMT and related inherited peripheral neuropathies with a significantly ($p$<0.001) higher prevalence rate for CMT1 subtype of 10.61 per 100,000.[94] Nonetheless, there are major prevalence variations, compared on a geographical or population level.[95] The highest CMT prevalence rate has been reported for Norway of 82.3 per 100,000, the lowest in Northern Ireland for 3.1 per 100,000.[94, 96, 97] In IBM, estimations for the prevalence range between 4.5 and 9.5 per million and in elderly over the age of 50 up to 139 per million as the most common myopathy in that age group.[98, 99] The prevalence of IBM is difficult to estimate, since it has increased over time, not only due to different classification systems in the past. Prior to higher awareness and prognostic performance in the last few years, IBM was a rather underestimated IIM.[98, 100] According to the definition of the EU, CMT and IBM could therefore both be subsumed under the term 'rare diseases', referring to prevalence rates of less than 5 per 10.000.[101] Pivotal for the topic under investigation in this thesis, the EU attributes a high complexity to rare diseases.[102] However, also national health ministries like in Germany are increasingly aware of these almost 4 million German patients with rare diseases (30 million estimated in the EU) who have to cope with their often life-threating and chronic disabling diseases.[103]

Transferring these outlines to NMDs, complexity is also expressed in the fact that IBM and CMT (within the different disease types) share the characteristic of heterogenous clinical phenotypes.[104, 105] Moreover, both diseases typically show a slow progressive disease course.[100, 106–108] Whereas the first manifestation of **symptoms** in CMT could already be present in childhood to adult age, the onset in IBM is by definition only from the age of 45 onwards and mainly affecting men in a 3:1 ratio.[107–112] Even though the disease severity and onset or the occurrence of symptoms are heterogenous in CMT, the most associated symptoms are listed hereinafter in order to better understand the patient burden.[113] CMT affects peripheral nerves and causes motor and sensory neuropathy, which leads to symmetric distal paresis. During the slow progression of most CMT forms, the peripheral weakness and atrophies begin in the feet as well as in the upper extremities in the hands. As a result of motor

neuropathy, fine motor skills deteriorate. The patient's increased inability to feel sensory stimuli (e.g., cold, heat) or decreased proprioception are due to sensory neuropathy. Curled toes (hammertoes) or fingers, as well as high arches are common structural deformities. Other symptoms are altered tendon reflexes, gait abnormalities (e.g., steppage gait) and seldom scoliosis, blindness or hearing loss.[90, 91, 113] Since IBM constitutes the major part of this thesis, a more in-depth overview of the symptoms and clinical presentation in IBM is provided in the following. In IBM, certain proximal and distal muscle groups are affected asymmetrically, such as quadriceps femoris and finger flexors resulting in muscle weakness.[114] It has been reported that IBM patients experience greater weakness and fatigue than other NMDs (e.g., PM, DM, FSHD).[115, 116] As a consequence of muscle weakness, falls are reported frequently by 60 % of IBM patients, although the concomitant impact on ADL or other patient-relevant outcomes is still scarcely researched.[114, 117] During progression, the aforementioned physical limitations make it difficult or impossible for IBM patients to stand up from a chair or climb stairs.[118] Further, an often underreported initial symptom is swallowing problems (dysphagia).[119–121]. Several studies have collected data on the frequency of dysphagia in IBM, whereupon 40 % of IBM patients reported swallowing problems at the point of diagnosis, and 60 % after 7 years of progression up to a maximum of 80 %.[106, 122–128] Associated causes of deaths in IBM are consequences of dysphagia, often resulting from cachexia, malnutrition, aspiration or pneumonia.[109, 110, 114, 129, 130] However, IBM and CMT are in general not associated with a significantly reduced life expectancy.[105, 110, 114, 131]

For the context of this thesis, it is of importance to note, that the explicit **disease mechanisms** in IBM are not yet entirely understood.[88, 132] There have been considerable discussions about the molecular etiology in the recent years regarding the inflammatory involvement and other underlying pathological factors in IBM. Typical characteristics are therefore degenerations in the form of rimmed vacuoles in muscle fibres and activity of T-cells.[88, 133–136] In CMT, most patients underly an autosomal dominant inheritance, and less frequent are an autosomal recessive inheritance or X-linked disorders (CMTX).[108, 137] To date, over 100 genes associated with CMT and similar disease forms are known and mutations have been identified in PMP22, MPZ, GJB1, as well as MFN2, in the majority of the CMT population.[96, 105, 107, 138, 139] By comparing CMT and IBM regarding their disease mechanisms on a high level, CMT is an inherited disorder, whereas IBM is sporadic. Despite some commonalities,

both NMDs cause different clinical pathways in diagnostics and treatments as briefly outlined in the next paragraph.

Recommended **diagnostics** in IBM comprise the thorough evaluation of clinical symptoms, laboratory assessments (especially creatine kinase), broad assessments of myositis-specific auto-antibodies, histopathological assessments within muscle biopsy, electromyography, and muscle MRI.[49, 140] The first diagnostic criteria for IBM were introduced by Griggs et al. 1995.[141] Meanwhile, these and other outdated criteria have been replaced by the latest diagnostic criteria of the European Neuromuscular Centre (ENMC).[112, 142] These ENMC criteria differentiate between three disease classifications in IBM: clinico-pathologically defined IBM, clinically defined IBM and probable IBM.[112] These classifications differ by the number of simultaneously present clinical features (e.g., extent of weakness regarding knee extension, hip and finger flexion, shoulder abduction), laboratory features (creatine kinase level) and pathological features (e.g., rimmed vacuoles, endomysial inflammatory infiltrate).[112] For IBM patients, the process of diagnosis often entails a long duration from the first symptoms until obtaining a *correct* diagnosis. Approximately five years of living with misdiagnoses (e.g., primarily PM) and in turn inadequate treatment approaches have been reported during this first phase of the patient journey.[99, 100, 116] At the time of diagnosis, reliable predictions about the individual progression of IBM are additionally complex.[143] Considering the high prevalence of dysphagia in IBM patients during the disease course, video fluoroscopy or flexible endoscopic evaluation of swallowing are further instrumental assessments to decrease the risk of death.[114] Turning to CMT, diagnostics are different due to the genetic etiology. Besides the typical symptom presentations of a neuropathy that have to be considered, nerve conduction velocity tests or electromyography should confirm the clinical impressions.[108] Furthermore, several algorithms are recommended for genetic testing in CMT to detect major gene defects (e.g., CMT1: especially PMP22, DNM2, GJB1, LITAF/SIMPLE, MPZ, NEFL), whereas whole-exome or whole-genome sequencing remain a challenge for a regular and structured uptake in clinical practice, e.g., due to uncertain reimbursement regulations in Germany.[108, 144–146] However, next-generation sequencing panels could effectively complement the future diagnostic landscape in CMT.[147] Additional medical imaging as MRI or ultrasound could further complete the diagnostics for the clarification of polyneuropathies and detect expanded nerve cross-sectional areas.[145, 148, 149] As there is a high number of multiple and partly seldom comorbidities and secondary

conditions in CMT, the corresponding diagnostics go beyond the scope of this thesis. In general, complex challenges in the diagnostic pathways of rare diseases such as CMT or IBM are amongst others: a long duration from symptom onset to diagnosis and consultations of numerous (non)-specialised health care professionals due to partial multiple organ involvement.[150] Thus, mean error rates of up to 40 % for diagnoses of rare diseases have been reported in the EU [151] Wasteful spendings of finite health care resources and grave psychological distress during diagnostic procedures put a strain on all stakeholders from the macro level (health care system) to the micro level of patients.[56, 150, 152]

Furthermore, rare diseases are additionally often accompanied by substantial delays in **treatments**.[150, 151] For both IBM and CMT there are currently no curative treatments available.[49, 88, 138, 153] The national S2k guideline provides recommendations for the management of myositis and thus for IBM [49]: Firstly, physiotherapy on a regular basis should be undertaken in IBM as an integral part of supportive therapy. Secondly, other recommendations for the symptomatic treatment are occupational therapy (especially for weakness in the hands and fingers) and speech therapy for dysphagia. Lastly, approaches with IVIg are also recommended in the current clinical guidelines, including an evaluation of the effectiveness after approximately six months to enable a decision whether to continue.[49] There is solely evidence showing that IVIg could improve or enhance progression in some patients, but not the overall course.[154–156] The treatment options for CMT have so far also been limited to symptomatic pharmacological treatment for pain management or surgical interventions (e.g., correction of foot deformities).[146, 157] CMT patients could also profit from genetic counselling as well as from physiotherapy and occupational therapy to increase or stabilise physical functions and HRQoL.[105, 146, 158–161] Assistive devices take on great importance for IBM- and CMT patients. In IBM, mainly walking aids are common, beginning with crutches or canes up to electric wheelchairs. There has been some discussion as to what extent assistive devices could mark relevant points of disease progression.[109, 118, 129] A long-term study from Cox et al. (2011) identified a mean duration of 11 ± 5 years in IBM patients from symptom onset to using a walking stick and 16 ± 4 years to using a wheelchair, respectively.[110] Walking aids, but also orthoses (especially ankle-foot orthoses), are fundamental in the clinical management of CMT patients.[161] So far, some investigations have been undertaken about the potentials of orthotic interventions in IBM- and CMT patients. Thus, bracing could prevent falls, minimise injuries or improve walking

economy.[162–164] Registered and currently recruiting studies of innovative treatment approaches in IBM (e.g., drug ABC008, trial NCT04659031) and CMT (e.g., drug PXT3003, trial NCT05092841) have attracted considerable attention from both scientific and clinical audiences and provide hope for the patients and their families.[107, 138, 153, 165–168]

Due to the rarity of IBM and CMT and the complexity of their diagnostic and therapeutic pathways, patient registries play a central role from an HSR perspective, especially for prevalence estimations, patient recruitment, and the pinpoint dissemination of patient information.[169, 170] In addition, while large scale RCTs are hardly possible in rare diseases, registries could provide valuable data for the approval processes of orphan drugs in order to show retrospective effects. Therefore, patient registries are a target field of the European TREAT-NMD network for rare NMDs, which aims to develop innovative treatments for this patient population.[68] To ensure the diagnostic accuracy of the IBM- and CMT patients included in the empirical studies of this thesis (research papers #2,3,4), the German CMT patient registry (www.cmt-register.de) and IBM patient registry (www.ibm-registry.org) were utilised for patient recruitment. Inclusion criteria of the registries are, on the one hand, the ENMC diagnostic criteria in IBM [112] and, on the other hand, a genetically confirmed diagnosis of CMT. In general, the medical context of IBM, CMT and NMDs outlined the basis of this thesis and the research papers, as they demonstrate examples of complex care situations in HSR and IS.

## 2.2 Patient-Reported Measures in Descriptive Health Services Research

A vital thematic focus of this thesis is HSR, precisely the *description* of aspects regarding actual complex care situations along the patient journeys of NMDs. This section provides an overview of the selected outcomes under investigation in the research papers, with the application of theoretical frameworks and appropriate assessment methods. By definition of the German Medical Association, descriptive HSR aims to describe influences on, as well as the processes and the results of the health care made available to patients by scientific methods.[171] The abovementioned desired patient-centredness in HSR studies can methodologically be fostered by respecting the threefold graduation of participatory health care research according to Wright et al. (2021) [172]. The first level, 'non-participation' is understood as exploiting or using study participants and instructing them to do something specific (e.g., taking part in an intervention). The preliminary stage to participation, as the second level, comprises involving, consulting or informing relevant stakeholders in health care, such as patients. Actual participation, as the third level, is characterised by letting stakeholders participate in decision making and giving them responsibilities. Beyond that, completely self-organised research projects by patients or other stakeholders can express the highest level of participation.[172–174]

Applied to the studies of this thesis, patients (e.g., via the CMT and IBM patient registries) and patient organisations (e.g., the German Association for Patients affected by Muscle Diseases, DGM) were primarily informed and consulted (preliminary stage prior to participation) within the research projects. However, overall there is only scarce evidence for the prioritisations of patient-relevant outcomes in rare diseases and the respective PROMs and PREMs.[175] To aim for a high level of participation and considering the aforementioned lack of evidence in rare diseases at this point, a sequential mixed methods approach was applied in this thesis to explore and understand relevant outcomes and experiences directly from the patient's view.[176] Due to this stepwise approach, focal points of relevant aspects of the patient journey in NMDs were initially identified and then investigated in-depth. The advantages of inductive qualitative methods and correspondingly adapted deductive quantitative methods should allow the patient voices to set priorities via the scientific research process. The range of methods in HSR covers descriptive, analytical and evaluative qualitative and quantitative study designs.[171] In the research papers referred to in thesis explorative qualitative interviews and

quantitative cross-sectional studies were applied for the purpose of describing PROs and PREs within complex care situations (Figure 1).

In order to precisely contextualise the following theoretical considerations precisely, it is further necessary to understand the term burden of disease. The term is generally meant to specify the overall consequences, such as costs or aspects of health, of a disease or a number of diseases by considering the respective disabilities in society.[177] It can be subclassified further into clinical burden (e.g., morbidity), humanistic burden (e.g., HRQoL) and economic burden (e.g., COI).[178, 179] From the outcome perspective in HSR, HRQoL is an eminent construct of humanistic burden in NMDs, as many NMD patients show decreased HRQoL during progression, not least due to the deteriorations of physical functions.[180–183] As politics and payers are addressees of HSR, transparency in respect of the economic burden or COI, respectively, is beneficial for the setting of priorities in research agendas and customise the service offered on the basis of unmet patient needs.[184] Accordingly, empirical data of HRQoL and COI were collected solely from research papers #2–4 with direct reports from the patients to understand aspects of the burden in IBM and CMT within their complex care situations.

Furthermore, several models are used in HSR to explain and understand the environment and patient-centred variables, such as outcomes or health behaviour, which influence the complex health care situations.[2] A persistent theme in the context of patient-centredness in HSR is the behaviour of patients.[2, 185] According to the modified Behavioral Model of Health Services Use according to Andersen (1995) [185], the health behaviour of patients is, for example, expressed by their actual use of health care services and dynamically influenced by the patient outcomes as well as predisposing characteristics, enabling resources or needs. Taking the aforementioned burden of disease into account, the variables and influencing factors of health behaviour are crucial to alter the economic and humanistic burden for society. In respect of the briefly outlined relevance and relationships, the research papers of this thesis aimed on the one hand to explore complex care situations with inductive-deductive methods truly and directly from patients. On the other hand, they aimed to integrate dynamic and interacting variables within the care situations in order to also understand the economic and humanistic burden from a behaviour-based perspective. Figure 3 depicts an overview and gives examples of which variables were collected in the IBM and CMT patient populations in the research papers #2–4.

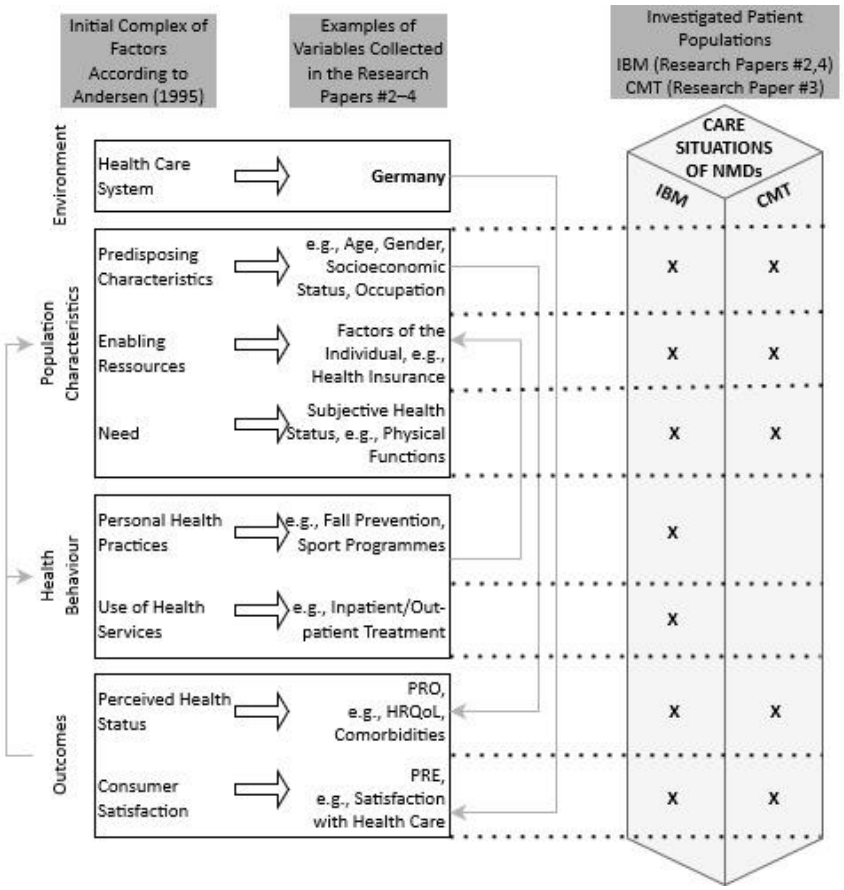


***Figure 3:*** *Investigated aspects of complex care situations in NMDs structured according to the Behavioral Model of Health Services Use according to Andersen (1995) [185]. Author's presentation based on Andersen (1995) [185].*

In virtue of a robust mixed methods design, it is indispensable to firstly identify the status quo in the literature and then to select empirical methods and redefine the research foci.[176] Research paper #1 provides a first overview of the existing evidence for the HRQoL and mental health in IBM patients as **PROs** of the perceived health status (cf. Figure 3). To be precise, a mixed methods systematic literature review was conducted by combining data from both qualitative and quantitative studies and reporting them narratively.[186] In view of the expected rather low body of evidence, the results were extracted and categorised broadly in the three dimensions of HRQoL according to the definition of the World Health Organisation (WHO). Hereafter, physical, social and psychological HRQoL are subsumed as a subset of quality of life when influenced by medical interventions or diseases.[187, 188] The results from the included studies of the review suggest that rigorous determinants of patient-reported HRQoL and mental health in IBM are not extensively researched so far. Moreover, the PROMs applied and the HRQoL and mental health values of the included studies varied, and a related disease-specific PROM for HRQoL in IBM could not be found. Although IBM seems to mainly

impair physical HRQoL, limitations of psychological HRQoL have also been reported.[189] By contrast, some other studies about HRQoL and mental health in NMDs have identified that the limitation of emotional or psychological aspects do not significantly correlate with disease severity or disease duration. Thus, the perspective of resilience is increasingly relevant.[115, 181, 183, 190, 191] As an example, Graham and Rose (2017) employed the Leventhal Self-Regulatory Model [192] and the Psychological Flexibility Model [193] to better understand the life satisfaction in male patients diagnosed with Duchenne muscular dystrophy (DMD).[190] The authors concluded as a hypothesis for further research that DMD patients with a higher life satisfaction seem to better accept challenging emotions and were more able to realise meaningful activities.[190]

The results and respective discussion of research paper #1 was the foundation for an in-depth qualitative interview study of the HRQoL, as PRO, and experiences about the care situation, as PRE, along the IBM patient journey (research paper #2). Thereby, the theoretical view also focused on resilience research approaches during the content analysis of the interviews with IBM patients. After an open inductive paper-pencil coding, in the second step of the overall three steps of content analysis the different cases were contrasted in order to identify commonalities and differences between the perceptions of HRQoL and care situations.[194] It appeared that the phenomenon of social support within a dynamic resilience process could be a relevant factor to buffer the distress of this chronic and progressive IBM disease in terms of HRQoL but was also perceived as a relevant patient-reported factor for the individual care situations. To structure the interview material in an inductive-deductive way during the last step of the analysis, two main frameworks were applied: the Throughput Model of HSR of Schrappe et al. (2017) [2] for the description of the different phases in the course of the IBM patient journey regarding input, throughput, output and outcome (HRQoL) factors as well as the Dynamic Network Approach of Resilience by Kalisch et al. (2019) [195] for representing the dynamic and interacting phases of HRQoL.

To date, there are several definitions according to which a person is considered to be resilient and numerous suggestions regarding how to operationalise and measure resilience.[196, 197] The essence of resilience reflects the phenomenon that, although a person experiences extreme physical or psychological burden, their mental health is either only temporarily limited or not limited at all.[198–201] In recent years, considering resilience as a dynamic process has attracted attention, as it not only sees resilience as an outcome and less as a static enabling

resource of a person.[198, 202–205] Kalisch et al. (2019) published a hybrid symptom- and-resilience-factor network firstly in order to mathematically illustrate the process-related complex mechanisms of mental disorders from a time-varying perspective with interactive influences and secondly in order to draw consequences and formulate demands for resilience research.[195] For the content analysis in research paper #2, solely the conceptualisation of the dynamic network models outlined were translated and adapted to the appraised care situation and the HRQoL by IBM patients. Here, the frameworks used should foreground the reported emotional and psychological issues along with the physical progression in IBM. The construct of social support via informational, emotional and practical support underpinned the 'phenomenon' of this qualitative study, as it facilitates to describing and understanding the research into HRQoL along the IBM patient journey.[206]

So far, the literature has already described mainly physical aspects suggested to be patient-relevant factors of a general HRQoL assessment in IBM.[189] A few IBM-specific PROMs have even been developed to measure the functional aspects (= need; subjective health status, Figure 3) with scales in IBM. For example, in 2019 the updated version of the Inclusion Body Myositis Functional Rating Scale (IBMFRS) was published and subdivided into a scale for upper limb function (IBMFRS-UL) and lower limb function (IBMFRS-LL) due to the earlier improper fit to the Rasch model aiming to describe clinical utility and validity.[207] However, the IBMFRS is no PROM as it is clinician-administered.[207] By contrast, the sIBM Physical Functioning Assessment (sIFA) is to date the only available disease-specific PROM for IBM patients. Moreover, its development followed the US Food and Drug Administration's guideline for PROMs [27].[208] In recent years, the Myositis Working Group and International Myositis Assessment & Clinical Studies Group (IMACS) have endeavoured to select suitable PROMs for patients diagnosed with IIM, forming the standard PROMs set 'Outcome Measures in Rheumatology' (OMERACT).[209–211] Nonetheless, within the respective evaluation study of seven PROMs regarding content validity and comprehension in the domains physical function and activity as well as pain and fatigue, IBM patients were excluded.[209] This suggests an underrepresentation of IBM within PROM developments for the IIM disease group and highlights the gap of holistic PROM developments that integrate, besides physical, also psychological and social aspects in IBM.

A different methodological focus, and not the hypothesis-generating aspect of qualitative research as in research paper #2, but descriptive and explorative quantitative methods were

utilised in research paper #3. To assess the HRQoL in CMT quantitatively, a questionnaire was used that built upon several preliminary qualitative and quantitative work.[61, 212] As PRO, HRQoL was assessed with the EuroQol five-dimension questionnaire (EQ-5D™ is a trade mark of the Stichting EuroQol Research Foundation) as a generic PROM. The EQ-5D is classified as a PROM by using patient preferences within the questionnaire and emphasising a ranking of 3,125 ($5^5$) different health states.[213] Further, it uses 5-point scales to measure health-related problems in the dimensions: mobility, self-care, usual activity, pain/discomfort, anxiety/depression. A visual analogue scale (EQ-5D VAS) serves as a further PROM to assess the perceived health state on a scale from 0 to 100 (worst to best).[214, 215] To utilise quantitative HRQoL data for HSR, it is not necessary to develop specific PROMs for HSR.[213] The EQ-5D is a recommended standard PROM to use in HSR.[213] Therefore, it is helpful to better understand the concurrent assessment of physical, social and psychological dimensions of HRQoL in CMT patients within their care situation in the German health care system. In addition, cost-benefit-assessments of future therapies in CMT could also profit from such standard EQ-5D index values when conducting economic analyses.[184] Since the data collection in 2015 within the cross-sectional study reported in research paper #3, mainly the development of two PROMs regarding the HRQoL in CMT has been reported. Firstly, the Charcot Marie Tooth Health Index in 2018 [216] and secondly, the Pediatric Charcot-Marie-Tooth Disease Quality of Life Outcome Measure in 2020 [217]. The different progress of PROM developments in CMT and IBM, is comprehensibly exemplified by the European-wide PROMs Repository 'ERICA'.[218] Unlike the very generic PROQOLID™ online database [219] for clinical outcome assessments, ERICA aims to identify and ultimately standardise PROMs for rare diseases in one database and thus provide a link to PROQOLID™.[218] No entries are currently available for IBM, other than for CMT, comprising the already mentioned Charcot Marie Tooth Health Index and Pediatric Charcot-Marie-Tooth Disease Quality of Life Outcome Measure (last update of the repository: 30th August 2022).[218] Overall, within the study of research paper #3 except for patients with HNPP, no differences have been found regarding the HRQoL in CMT subtypes by using the EQ-5D assessment.

At this point, a brief outline of the assessed **PREs** is appropriate to again take advantage of mixed methods assessments in HSR in order to understand the complexity in the care situations of NMDs. As illustrated in Figure 3, the satisfaction with health care and health insurance, respectively, was assessed quantitatively and qualitatively in two different patient populations

(CMT in research paper #3, IBM in research paper #4). To measure the PRE variable satisfaction, rating-scales were applied in combination with free-text boxes to supplement the quantitative measures with in-depth information and further suggestions for improvements from the patient's point of view. The Institute for Quality Assurance and Transparency in Healthcare (IQTiG) differentiates between two approaches to gathering patient-reported data. Hence, reporting approaches as PROMs and PREMs mainly gather data by collecting the intensity or frequency of particular events (e.g., symptoms). Rating approaches are meant if patients are requested to rate their disagreement or agreement with a certain given statement.[220, 221] In fact, this shows once more how various and granular forms of patient-reported measures are described and used in actual practice, as illustrated in the IQTiG's methods recommendations, the basis for fulfilling their legal mandate for the development of quality in the German health care system.[220] Above all, for the first time the goal was to describe the overall satisfaction with German health care services for CMT and IBM patients and satisfaction with health care insurance in IBM patients, respectively. Consequently, a simple, less specific rating measure was appropriate. The narrative summary of the qualitative data in the free-text boxes revealed indications for further relevant PRE dimensions.

Lastly, to complement the insights gained into the complex care situations from the perspective of humanistic burden, research paper #4 focuses more on the economic burden of IBM due to the collected patient-reported data on the **resource utilisation** and subsequent estimated **COI**. Comprehensive and transparent cost data are particularly needed for economic evaluations, which is why a thorough selection of the data basis and -quality is crucial.[184] The Institute for Quality and Efficiency in Health Care (IQWiG) concluded in its rapid report from 2020 about the "*Concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V (SGB V)*" that for the purpose of benefit assessments statutory claims data are so far and in the near future no feasible alternative for deriving routine practice data. The IQWiG instead therefore highlighted the need for primary research and the utilisation of patient registries for data collection.[70] When examining IBM, it is necessary to reflect the clinical complexity of this rare disease (cf. Section 2.1) that impedes a simple top-down approach for cost estimation, while the International Statistical Classification of Diseases and Related Health Problems (ICD) codes are currently still too general for both required clinical and patient-relevant subgroup analyses.[121, 222] Before selecting the database (primary or secondary data), the perspective of cost

estimation has to be defined. To ensure a holistic representation of all direct costs incurred regarding IBM and to avoid underestimating the presumed high indirect costs, a societal perspective was specified for the COI study within this thesis.[223, 224] This selection is supported by the recommendations of the IQWiG, the Hanoveran Consensus and the health economics literature.[225–228] After defining the perspective for the identification of utilised resources, the next steps in COI studies are: the measurement of the utilised resources, the evaluation of unit prices for these resources, and finally estimating the COI.[184, 229] To accurately identify and understand the actual care situations and thus resource utilisation from the IBM patient's point of view, a micro-costing approach was used in this COI study. This bottom-up approach guarantees the inclusion of a detailed and flexible data collection and estimation.[229] The clinical picture of IBM justifies the choice of the micro-costing approach, since the following criteria are met: frequent use of cost-intensive resources (e.g., IVIg), presumed heterogenous resource use, and large differences in intervention alternatives.[225, 230] For all of these reasons, when considering complex disease patterns as NMDs, individual cost estimates through micro-costing are more comprehensive. Average resource consumptions of the disease, as well as productivity losses, can be described more accurately and biases due to comorbidities can be better delimited.[231] Although some limitations of this approach must be mentioned (e.g., selection- or recall bias, expensive and time-consuming data collection), the certainty of IBM diagnosis through the IBM patient registry and simultaneous collection of other PRO and PRE variables for subgroup analyses ultimately excluded the use of secondary data.[232, 233] The applied survey for this cross-sectional registry study was based upon the preliminary work of other COI studies in SMA, DMD, CMT and Becker muscular dystrophy within the German health care system.[61–63] The online questionnaire was customised for the IBM disease characteristics along the iterative research process with the help of the literature review (research paper #1), qualitative interviews (research paper #2) and researcher triangulation (physicians, health economists, health services researcher).

To recap, the research papers in this thesis concentrate mainly on investigating patient-reported health behaviour and outcome variables in the actual complex care situations in NMDs (Figure 3). At the same time, patient characteristics, enabling resources and needs (e.g., comorbidities by using the German version of the Self-Administered Comorbidity Questionnaire, SCQ-D) were also collected and integrated into the exploratory quantitative and qualitative analyses in order to better describe the care situations. Whereas the research papers

#1,2,4 formed a serial sequential design in the context of IBM, in the context of CMT research paper #3 supplemented preliminary mixed methods work.[61, 212] Although exploratory, for the first time the findings provide insights into patient-relevant variables within the actual care situations in CMT- and IBM patients enrolled in the respective patient registries in Germany.

## 2.3 The Identification of Barriers and Facilitators – Key Success Factors for Effective Implementation

During the research process for the first four papers and by interpreting and discussing the results, it was suggested that so far little effort has been devoted to the implementation research of innovative telemedicine interventions in NMDs. Research paper #5 concludes the exploration of complex care situations in NMDs in this thesis by providing an overview of the actual use of telemedicine and the respective barriers and facilitators of implementation in NMDs. Arguments concerning why it is important to thoroughly understand the implementation of interventions in clinical practice are presented in this section. Further details are also given for the applied frameworks and taxonomy in the systematic literature review in research paper #5.

According to the review findings of Bauer and Kirchner (2020), IS should be incontrovertibly fostered in health politics for the following reasons.[234] Proving the effectiveness of an intervention alone does not lead to its implementation in daily clinical practice. Not only are less than half of clinical innovations actually implemented in clinical practice, their successful uptake usually takes 17–20 years.[235–238] Factors influencing the adoption or refusal of an effective intervention are both diverse and complex in the respective context.[234] In addition to the abovementioned goals of IS (cf. Section 1), frameworks and models have been established to put forward theories in respect of successful intervention uptake by using mainly explanation approaches of behavioural and social science. For instance, typical frameworks are the Promoting Action on Research Implementation in Health Services (PARIHS) of Rycroft-Malone (2004) [239], the Normalisation Process Theory (NPT) of May and Finch (2009) [240], and the CFIR of Damschroder et al. (2009) [42]. However, for IS, critics attribute a lack of unambiguous definitions, utilising “middle-range theories” and promoting a normative conception in IS.[241] Nevertheless, there is growing awareness in this young research area that the more than 60 existing IS frameworks still need to be further refined in terms of their content and their recommendations in order to utilise and select these in research projects.[39, 242, 243] Turning away from this meta-discourse to the research object of research paper #5, the well-established and validated CFIR framework was used to structure barriers and facilitators of the actual telemedicine interventions in NMDs.[42] Since the CFIR was established, various practical tools have been generated to support the evaluation of implementations or plan

implementation studies (e.g., interview guide tool).[244] For the usage of the CFIR in research paper #5 it is important that the utilisation of the CFIR is appropriate in all stages of an implementation (from pre- to post-implementation). Thus, the CFIR can additionally serve as a structure to summarize the results of different study types and to provide suggestions in a standardised manner.[42, 245] Five domains constitute this framework: characteristics of the intervention (innovation), outer and inner setting, and characteristics of the individuals involved and the implementation process.[42] The comprehensive description of the five core domains can be found elsewhere and goes beyond the goal of this section.[41, 42, 244] As depicted in Figure 4, the systematic review in research paper #5 included, as innovations under investigation, all telemedicine interventions according to the taxonomy of telemedicine by Bashshur et al. (2011) [246]. The CFIR domains with their respective constructs were used to design the extraction grid accordingly for the narrative analysis of the studies included in the review.

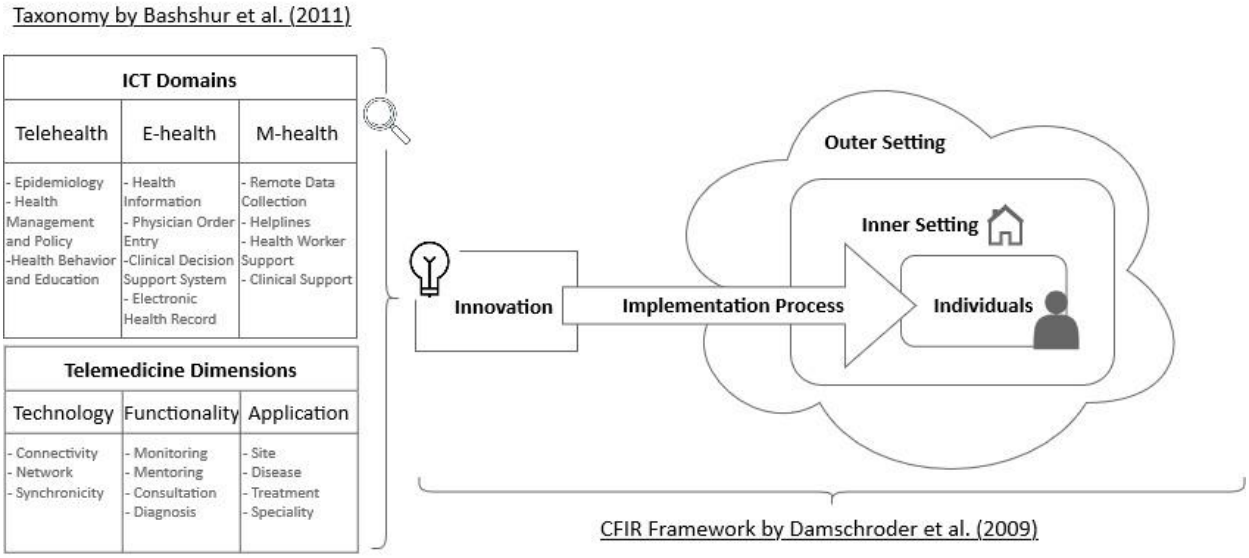


***Figure 4:*** *Applied taxonomy of telemedicine of Bashshur et al. (2011) [246] and domains of CFIR Framework of Damschroder et al. (2009) [42] in the Systematic Review of research paper #5. Author's presentation based on Khan (2021) [247].*

The systematic review in research paper #5 aims to provide a precise overview of telemedicine in NMDs for the first time, in the face of the fragmented literature of the individual diseases. Moreover, the COVID-19 pandemic acted generally as a driver for telemedicine interventions to encourage interest in recent major developments and emerging new tools. The German study CORONA-MONITORING lokal (CoMoLo) analysed population-based data of the Robert Koch Institute from the second to the fourth quarter of the year 2020 and showed that only

2 % (95 % CI 1.6 – 2.4) of all included participants (*n* = 7,873) utilised consultations via telemedicine and 6 % (95 % CI 3.9 – 9.5) of the participants who refused to consult a doctor while experiencing symptoms (*n* = 708), respectively.[248] Data from later stages of the pandemic show a dramatic increase of utilisation even in low- and middle-income countries.[249] General barriers and facilitators regarding the international uptake of digital health solutions were described by Bratan et al. (2022) and differentiated into socio-economic, cultural, regulatory and technological aspects.[250] Such broad categories make it difficult to provide nuanced recommendations for action.

To tailor implementation strategies that aiming to increase the uptake in an individual complex setting, the theory-based CFIR guide structures the assessment of potential and actual facilitators and barriers.[244] Understanding the underlying barriers and facilitators for an implementation is essential in learning and reactive health care systems to promote behavioural change and profit from effective innovations.[251] In 2022, the WHO published the Consolidated Telemedicine Implementation Guide for policy decision makers and responsible persons for telemedicine implementation, in which a landscape analysis and the assessment of enabling factors of the implementation environment are crucial steps towards planning successful implementation strategies.[252] Transferred to the context of the umbrella term of NMDs with its over 850 different diseases (cf. Section 2.1), it is presumably almost impossible to tailor implementation strategies to every one of these single diseases and also to the individual settings. Nevertheless, a systematic review with an identification and transparent description of these implementation factors can help to initially raise awareness for typical barriers to telemedicine in the context of NMDs and also can serve as an incentive to combine future effectiveness studies with implementation studies.[251]

Transparency of the actual status quo of versatile and complex care situations regarding telemedicine approaches in NMDs results by using clear definitions and taxonomies and thus the taxonomy of telemedicine by Bashshur et al. (2011). As mentioned above, this taxonomy was used firstly to differentiate between the domains of ICT as shown in Figure 4. Secondly, the telemedicine interventions identified were analysed according to the dimensions of telemedicine, namely technology, functionality and application.[246] On a very high level, ICT implies delivering health care by overcoming distances between either provider and provider, provider and patients, or as a source of information for both stakeholders.[246] The WHO's definition of electronic health (eHealth) also highlights the cost-effectiveness and security of ICT

to optimize health care, and the WHO has already been accorded eHealth status in the National eHealth Strategy Toolkit (2014) as a fundamental part of responsive health systems.[253] The term telehealth has often been used as synonym for telemedicine and interchangeably, which is why the upcoming terms of eHealth and mobile health (mHealth) complicated the precise delineation of technologies.[246] By respecting these terminological hindrances and the necessary practical relevance of accuracy, the taxonomy of Bashshur et al. was used to analyse telemedicine and its domains. In conclusion, a lack of research was identified for implementation studies in NMDs. For the mainly reported mHealth solutions in NMDs, the respective barriers and facilitators were only stated in the dimensions 'intervention' and 'individuals involved'.

To summarise, the research papers of this thesis, the exploration and understanding of actual complex care situations in NMDs may be a suitable initial basis for further hypothesis testing in HSR and IS. Here, attention has to be drawn to the ongoing refinement of underlying theories (e.g., behavioural models) and implementation of innovations to firstly understand the patient's perceptions and thus varying aspects of health behaviour, secondly, to profit from effective interventions, and lastly to relieve the disease burden of patients and their caregivers. Care situations in NMDs are complex, dynamic and in some cases unknown due to their rarity. By using mixed methods and in-depth use cases of NMDs, this thesis contributes to a better understanding of national as well as international actual care situation in NMDs. In this broad field of NMDs, the thesis more specifically offers starting points for need-oriented improvements in medical practice and health policy and need-oriented agenda setting of research priorities in HSR and IS. The following Section 3 provides a brief summary and an outlook for future research.

# 3. Summary and Future Research[3]

## 3.1 Summary

Five research papers are included in this cumulative thesis, representing an intersection of HSR and IS in the context of complex care situations in NMDs. Although a higher patient-centredness and outcome orientation is observed in medical research and practice, disease-specific research relating to PROs and PREs and regarding the development of PROMs and PREMs is lacking for rare diseases and accordingly in NMDs. An in-depth and comprehensive description of patient-relevant outcomes and experiences lays the basis for the development of innovative therapeutic and supportive approaches that matter for the health ecosystem. General aspects of PROs, like HRQoL in chronic diseases, have now been documented extensively. However, there is considerable variation in the available amount of evidence between the several NMDs regarding HSR of PROs and PREs. Moreover, the economic burden is often still not known for these heterogenous disease groups. Consequently, an unawareness of the economic relevance acts as a hindrance for transparent agenda setting and promising investments from health politics, research and the medical industry. The scarcity of resources in the health care sector demands the implementation of need-oriented, sufficient and effective health care services. To promote the actual uptake of effective innovations, like telemedicine in NMDs, the understanding and description of barriers and enabling factors are crucial for defining context-oriented implementation strategies. Consequently, this thesis examines the complex care situation for NMDs. Specifically, the exploration and description of PROs and PREs and the estimation of COI were investigated in the two use cases IBM and CMT. Additionally, the status quo of telemedicine was researched for the entire group of NMDs. The use of theory-based structures of HSR and IS for the mixed methods analyses contributes to the reduction of the complexity of the care situations in NMDs.

For the presentation of the complexity within the care situations of NMDs, Section 2.1 provides an overview of the clinical background of NMDs (especially IBM and CMT) regarding prevalence rates, common symptoms, disease mechanisms and the status quo of recommended diagnostic and treatment approaches. The two chronic and progressive diseases IBM and CMT were selected from the complex NMDs as of the diseases under

[3] The content of this section is partly taken from the research papers included in this thesis. The citation style of the papers has been used in order to improve the readability.

investigation in research papers #1–4. In spite of the heterogenous characteristics of the respective patient populations in IBM and CMT, some commonalities can be identified. The background outlined in Section 2.1 further increases the understanding of which disease-related problems the patients, caregivers and health professionals are confronted with in their everyday life. In total, it is stated why it is important to pro-actively accelerate outcome oriented HSR and IS in such complex diseases.

In Section 2.2, the two examples of complex care situations in IBM and CMT are with reference to the exploration and description of patient-reported measures to illuminate phenomena like HRQoL, satisfaction with health care, or even the comprehensive COI. The use of mixed methods of HSR enables to gain insights into the various patient perceptions of their complex care situations and to generate new hypotheses from qualitative approaches and to assess selected factors quantitatively. Firstly, the results of research papers #1–2 suggest heterogenous and dynamical perceptions of IBM patients regarding their physical, social and psychological HRQoL and emphasise the role of social support within the patient-caregiver dyad. Secondly, the quantitative measurement of HRQoL in CMT identified no differences in HRQoL between the subtypes, except for HNPP patients with impaired HRQoL in contrast to the value set for Germany. Thirdly, rather good or very high satisfaction with health care in Germany was reported from 72.0 % of CMT patients in contrast to IBM patients, whereby 69.2 % reported very high or quite a bit satisfaction. Fourthly, the investigation of patient-reported resource utilisation and the respective estimation of COI in IBM (research paper #4) suggests heterogenous but considerable cost, notably direct costs. More precisely, the costs of pharmacotherapy and informal care underscore the relevance of efficient resource utilisation of high-priced therapies as well as the required awareness of the caregiver burden.

By researching the modifiable factors of the patient's health behaviour, further complex factors of telemedicine in NMDs were investigated with the application of theory based IS frameworks, as elaborated in Section 2.3. The heterogeneity of the results in research paper #5 again reflect the complexity entailed with the current use of telemedicine in NMDs. Telemonitoring and teleconsultations are the most frequently reported technologies. Barriers or facilitators for implementation have only been reported in the dimensions 'innovation' and 'individuals'. This cumulative thesis has practical implications for health care professionals to better understand patient-reported unmet needs, but also for health politics and medical

industry to set priorities and justify urgently needed investments to improve outcomes in NMDs.

## 3.2 Future Research

To conclude, in this cumulative thesis certain limitations must be noted and the results must be interpreted with caution. Therefore, it is important to have a clear understanding of the different possibilities and objectives of qualitative and quantitative research. As this thesis embodies methods of both research types, the different limitations as well as the consequences for future research have to be considered.

In respect of the medical context of complex care situations outlined in NMDs (Section 2.1), Section 2.2 encompasses feasible and adequate methods to assess patient-reported perceptions concerning factors which shape their resulting care situations. The systematic review in research paper #1 shows variations in the current use of PROMs to assess the HRQoL in IBM patients. The lacking disease-specific PROMs in IBM impede the valid identification of robust factors that determine the HRQoL. A holistic approach is needed to develop instruments that include, besides physical, also social and psychological dimensions. Furthermore, the literature is fragmented regarding the use of general PROMs to measure the HRQoL in IBM. Meta-analyses cannot be performed until the PROMs are varying or even absent. As a result, the ongoing efforts to provide NMD-specific recommendations for outcome measures are necessary and should be further specified for the individual diseases. The effectiveness of innovative therapies regarding PROs could only be demonstrated if current and future trials respect patient-relevant outcomes already during the planning of the study designs. Hence, the literature review served as a starting point for an in-depth qualitative study in IBM to explore the HRQoL along the patient journey. For the first time, a possible structure of the IBM patient journey in the form of four phases was suggested, representing the frequently reported good or stable HRQoL values in IBM patients in spite of suffering from an enormous physical burden. Nevertheless, due to the circular approach of qualitative studies and the selected IBM patient sample, the generalisation of the results is possible only to a limited degree. The qualitative analysis of the interviews and a narrative reporting have the advantage of precisely describing details and putting relevant issues into a wider context. For this reason, research paper #2 generates new hypotheses to test in future quantitative large-scale studies. At a glance, in the long term further research should not only investigate the HRQoL in IBM patients, but also in possible relevant influencing factors such as social support and resource utilisation. For the same reason the cross-sectional study in CMT (research paper #3) built upon previous

qualitative studies and, on the one hand, provided comparative values of HRQoL for future trials, and on the other hand valuable data for future economic cost-utility-measures of innovative therapies. Lastly, the assessment of resource utilisation and estimation of COI in IBM (research paper #4) complements previous evidence from claims data in the US health care system by also quantifying indirect costs in IBM for the first time. The results emphasise the economic burden in IBM and could intensify general research activities in IBM when comparing the tremendous cost to the cost of other diseases like SMA or DMD and CMT. While the bottom-up approach used offers the possibility of an accurate and precise cost estimation, the available recommendations in the health economic literature as well as the standard unit costs are at some points not in line with the highly dynamic and often changing current national legislation. The possible inaccuracies could be compared on the basis of future replication studies. Although high patient numbers included in the surveys and the guarantee of diagnostic certainty by recruiting through patient registries, the external validity is limited as all patients exclusively reported their perceptions within the German health care system. In addition, the patients listed in the registries could be more dedicated and favour a selection bias. However, some findings could be transferred to international care settings. Hence, the PROMs, PREMs and variable sets used can structure future international multicentre studies of HSR in rare NMDs.

Several conclusions can also be drawn from the systematic review of current telemedicine in NMDs (research paper #5). This first taxonomy-based narrative summary of this research topic indicated that mHealth solutions are the most frequently investigated telemedicine solutions. At this point it is important to note that the use of a different taxonomy for telemedicine could have resulted in other terminological classifications. Conflicts with other existing reports prevent one from making indisputable conceptual distinctions. Future research in telemedicine and digital health in general should therefore make use of accepted and consistent taxonomies. Besides pharmaceutical research with the aim of discovering new therapies to mainly relieve the patient's physical trajectories, patient-centred HSR and IS studies could further initiate the implementation of effective digital solutions in regard to preventive and supportive services. By bridging the time until innovative breakthroughs of the pharmaceutical industry are ready for the market, PRO and PRE assessments and the descriptions of the current barriers and facilitators for implementation could create transparency and reduce the complexity. Speaking not only for the German context, the uptake of adequate PROMs and PREMs, as

investigated in the first four research papers, could encourage the demonstration of positive care effects in future "'digital assistants' in the hands of patients" [22] and ensure their reimbursement. More intensive research activities regarding implementation studies in the field of telemedicine for NMDs could ultimately improve the quality of care by an accompanied stimulated adaptation and uptake of effective innovations. Combining the suggested unmet needs in NMD patients from research papers #1–4 (e.g., more disease-specific health care services) with the current use of telemedicine, effective digital solutions to relieve social, psychological and even the economic burden for patients and caregivers could inspire future product development.

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# 5. Appendix

## I. Index of Research Papers

**Research Paper #1: The Health-Related Quality of Life, Mental Health and Mental Illnesses of Patients with Inclusion Body Myositis (IBM): Results of a Mixed Methods Systematic Review**

Senn KC, Gumbert L, Thiele S, Krause S, Walter MC, Nagels KH. The Health-Related Quality of Life, Mental Health and Mental Illnesses of Patients with Inclusion Body Myositis (IBM): Results of a Mixed Methods Systematic Review. Orphanet J Rare Dis. 2022;17 (1). doi: 10.1186/s13023-022-02382-x.

**Research Paper #2: Inclusion Body Myositis - Health-Related Quality of Life and Care Situation during Phases of the "Patience Journey" in Germany: Results from a Qualitative Study**

Senn KC, Thiele S, Gumbert L, Krause S, Walter MC, Nagels KH. Inclusion Body Myositis - Health-Related Quality of Life and Care Situation during Phases of the "Patience Journey" in Germany: Results from a Qualitative Study. Health Qual Life Outcomes. 2023;21(1):111. doi: 10.1186/s12955-023-02196-w.
Earlier version published: Patientenrelevante Faktoren der gesundheitsbezogenen Lebensqualität und Versorgungssituation bei sporadischer Einschlusskörpermyositis – erster qualitativer Teil einer Krankheitskostenanalyse im Mixed-Methods Design (25. Congress of Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.), digital, Germany, 2021.

**Research Paper #3: Health-related Quality of Life and Satisfaction with German Health Care Services in Patients with Charcot-Marie-Tooth Neuropathy**

Schorling E, Senn KC, Thiele S, Gumbert L, Krause S, Schreiber-Katz O, Walter MC, Reilich P, Nagels KH. Health-related Quality of Life and Satisfaction with German Health Care Services in Patients with Charcot-Marie-Tooth Neuropathy. J Neuromuscul Dis. 2022;9(1):211–220. doi: 10.3233/JND-210667.

**Research Paper #4: Cost of Illness in Inclusion Body Myositis – Results from a Cross-Sectional Study in Germany**

Senn KC, Thiele S, Kummer K, Walter MC, Nagels KH: Cost of Illness in Inclusion Body Myositis – Results from a Cross-Sectional Study in Germany. Orphanet J Rare Dis. 2023;18(1):337. doi: 10.1186/s13023-023-02902-3.

**Research Paper #5: A Systematic Review of Telemedicine for Neuromuscular Diseases: Components and Determinants of Practice**

Senyel D, Senn KC, Boyd J, Nagels KH: A Systematic Review of Telemedicine for Neuromuscular Diseases: Components and Determinants of Practice. *Submitted to: BMC Digit Health.*
Earlier version published: Eine systematische Übersichtsarbeit zu Telemedizin für neuromuskuläre Erkrankungen: Komponenten und Determinanten der Implementierungspraxis (26. Congress of Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e. V.), Essen, Germany, 2023.

## II. Individual Contribution to the Research Papers Included

Five research papers of different research groups and within different projects are included in this cumulative thesis. To disclose, this section provides further details about the research groups, projects and the author's individual contributions to augmenting each of the research papers.

Research paper #1 (Senn et al.) was presented in Section 2.2. Five co-authors contributed to this systematic review. Three clinical researchers, affiliated with the Friedrich-Baur-Institute, Department of Neurology of the Ludwig-Maximilians-University in Munich, contributed to the interpretation of the data and reviewed the manuscript for intellectual content. This was the starting point of my doctoral thesis and of a funded project concerning IBM in cooperation with the clinical colleagues from the Ludwig-Maximilians-University Munich and under the supervision of Klaus Nagels. I was mainly responsible for the concept of the literature search. Therefore, I conducted the comprehensive literature search and screened the studies together with a second independent reviewer. I analysed the included studies according to the three dimensions of HRQoL. Moreover, I drafted the manuscript and was responsible for the coordination of the valuable co-authors' comments and lastly for the submission process. Overall, I contributed substantially to this research paper as the first author.

Research paper #2 (Senn et al.) was presented in Section 2.2. The same five co-authors as in research paper #1 were involved in this qualitative study. This represents the second part of the funded IBM project, in which I was responsible for managing and undertaking the respective study. Besides the meaningful and valuable contribution of the registry physician in Munich to recruit suitable patients, I conceptualised the qualitative study design and developed the interview guide, all under the supervision of Klaus Nagels and Maggie Walter. Furthermore, I conducted all interviews face-to-face or via telephone and analysed the interviews by selecting and utilising two models of HSR and psychology. I drafted the manuscript and was again responsible for the coordination of the co-authors' comments and lastly for the submission process. The discussion of the findings with the other co-authors in the sense of triangulation was of great benefit for me in gaining an even deeper understanding of the IBM patient care situation. Once again, as the first author, my contribution to this research paper was substantial.

Research paper #3 (Schorling et al.) was presented in Section 2.2. This research work built upon preliminary work of a research group conducting a registry study in CMT in 2015. The cross-sectional study was also part of a funded project concerning CMT in cooperation with five clinical colleagues from the Ludwig-Maximilians-University in Munich. Early in my doctoral studies I was consulted after data collection and drafting of the manuscript and requested to contribute to the content of the manuscript based upon my experience in the field of HRQoL and was given the opportunity to strengthen my methodological research skills as well as knowledge in NMDs. I was considerably involved in the critical data interpretation, including the useful co-authors' comments in the manuscript and coordinating discussions about the presentation of the results. Lastly, I was also responsible for the submission process, which also included further text revisions during resubmission. Overall, I made a major contribution to this research paper.

Research paper #4 (Senn et al.) was presented in Section 2.2. This cross-sectional registry study in IBM patients completed the funded project in IBM in cooperation with the clinical colleagues from the Ludwig-Maximilians-University in Munich. Under the supervision of Klaus Nagels and Maggie Walter I adapted and developed the questionnaire items and conceptualised the quantitative approach. Thereby, I also suggested adequate PROMs and PREMs by referring to my previous research in IBM (research papers #1–2) and finally implemented the online questionnaire and compiled a paper version. Together with the registry physician, who significantly coordinates the dissemination of the questionnaire and was the contact person for the patients in case of questions, I was responsible for the operative data collection and study implementation. In addition, I conducted the statistical analysis and economic estimations of the COI and developed the manuscript draft and thus the presentation of the results. Again, I was responsible for the entire submission process and the inclusion of the co-authors' comments. Overall, again I had a substantial contribution in this research paper as first author.

Research paper #5 (Senyel et al.) was presented in Section 2.3. Building upon my scientific work of research papers #1–4 and the respective gained knowledge regarding the complex care situations of NMDs, I significantly contributed to a research collaboration with the Chair of Digital Health and Innovation, Department of Public Health at the La Trobe University in Melbourne, Australia. The systematic review in research paper #5 provided the theoretical foundation for a joint research project, which aimed at exploring the digital ecosystem of rare neuromuscular diseases (DiS-Rare) in Germany and Australia. I substantially developed the

study design and research questions for the DiS-Rare project under the supervision of Klaus Nagels and James Boyd. Accordingly, I also developed the research question for the systematic review and supervised a Master student in health economics to write the study protocol, conduct this review and finally create the research paper. In the role of a more experienced teaching and research assistant I discussed and selected the framework and taxonomy jointly with the Master student. To ensure methodological adequacy I undertook the second independent screening of the literature and was further involved in the discussion of the results. Finally, I contributed to the content of the research paper by multiple critical reviewing and commenting. The expertise from the Australian colleagues benefitted my knowledge of digital health and the provided valuable feedback to identify unmet needs in NMDs adequately. Once again, my contribution to this research paper was substantial.

## III. Research Paper #1: The Health-Related Quality of Life, Mental Health and Mental Illnesses of Patients with Inclusion Body Myositis (IBM): Results of a Mixed Methods Systematic Review

**Authors:** Senn KC, Gumbert L, Thiele S, Krause S, Walter MC, Nagels KH

**Published in:** Orphanet J Rare Dis. 2022;17 (1). doi: 10.1186/s13023-022-02382-x.

**Abstract:**

*Background:* Inclusion body myositis (IBM) is a rare neuromuscular disease (NMD) and effective therapies are not available. Thus, it is relevant to determine the health-related quality of life (HRQoL) in IBM patients including aspects of mental health and illnesses.

*Objectives:* To identify and summarize the assessment of HRQoL, mental health and illnesses in IBM, the major factors that determine and influence them as well as the respective influence of IBM in general and compared to other NMD as a systematic review.

*Methods:* We performed a mixed methods systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search was conducted within the databases PubMed, PsycINFO, LIVIVO and the Cochrane Database. Data were narratively summarized and categorized in the physical, psychological and social HRQoL dimensions.

*Results:* The systematic screening totalled 896 articles. Six studies were finally identified, comprising of 586 IBM patients. The applied patient-reported outcome measures (PROMs) varied. Quantitatively, the main physical impairments (e.g., weakness, functioning, role perception) were assessed using the general population or other NMD as comparators. Results on social and psychological HRQoL were frequently inconsistent. Qualitatively, psychological and social limitations accompanied IBM related physical deteriorations.

*Conclusions:* A research gap exists regarding rigour determinants of HRQoL and mental illness in IBM. In-depth qualitative studies could help to prepare the ground for the assessment of long term HRQoL data combined with appropriately focussed psychological PROMs advancing the understanding of the HRQoL in IBM throughout the course of the disease from a patient perspective.

*Keywords:* Health-related quality of life, Inclusion body myositis, Neuromuscular diseases, Mental health, Rare diseases

## IV. Research Paper #2: Inclusion Body Myositis - Health-Related Quality of Life and Care Situation during Phases of the "Patience Journey" in Germany: Results from a Qualitative Study

**Authors:** Senn KC, Thiele S, Gumbert L, Krause S, Walter MC, Nagels KH

**Published in:** Health Qual Life Outcomes. 2023; 21(1):111. doi: 10.1186/s12955-023-02196-w.

**Abstract:**

*Background:* To understand the health-related quality of life (HRQoL) in inclusion body myositis (IBM) from a holistic perspective on the background of a complex care situation. The focus was on how the patient journey may be structured over the course of this rare disease.

*Methods:* An exploratory qualitative study was performed via in-depth semi-structured interviews. Seven patients (males n = 5) with 2011 European Neuromuscular Centre (ENMC) IBM criteria from the German IBM patient registry were interviewed for this study. The dynamic network approach of resilience and the throughput-model of health services research were used to structure the qualitative analysis.

*Results:* Our results suggest that IBM patients experience the holistic HRQoL and care situation typically in four phases: (1) uncertainty about physical vulnerability until diagnosis, (2) promising treatment approaches, (3) self-management and dyadic coping, (4) weak body, busy mind and caregiver burden. The homophonous in-vivo code "patience journey" describes the frequently reported emotional perspective of the patient journey. Although the overarching theme of perceived social support varied throughout these phases, a reliable patient-partner-dyad may lead to improved HRQoL in the long-term.

*Conclusions:* New hypotheses for future quantitative research were generated to better understand the IBM patients' burden in the long term. The identified relevance of social support emphasizes the patients' need to handle IBM as manageable in medical settings. During exhausting phases of IBM progression, more effective care elements for patients and their partners could disclose varying needs. Strengthening multi-professional healthcare services via individualised informational, practical, or emotional support could improve HRQoL, especially since there is no curative treatment available so far.

*Keywords:* Health services research; Health-related quality of life; Inclusion body myositis; Qualitative research; Social support.

## V. Research Paper #3: Health-related Quality of Life and Satisfaction with German Health Care Services in Patients with Charcot-Marie-Tooth Neuropathy

**Authors:** Schorling E, Senn KC, Thiele, Gumbert L, Krause S, Schreiber-Katz O, Walter MC, Reilich P, Nagels KH

**Published in:** J Neuromuscul Dis. 2022;9(1):211–220. doi: 10.3233/JND-210667.

**Abstract:**

*Background:* Charcot-Marie-Tooth (CMT) neuropathies entail a large group of diseases with different gene mutation patterns, which produce heterogeneous phenotypes. Although health-related quality of life (HRQOL) is significantly impaired, a comprehensive assessment of HRQOL in CMT patients in Germany considering phenotypical heterogeneity represented a research gap.

*Objective:* The aim was to assess HRQOL and the satisfaction with health care in CMT patients in Germany.

*Methods:* CMT patients > 15 years with a genetically confirmed CMT subtype were recruited through a national CMT patient registry. HRQOL was assessed using the EQ-5D-5L questionnaire. Furthermore, subjective impairments in daily or work activities and satisfaction with health care were assessed using 4-point scales.

*Results:* HRQOL in CMT patients (*n* = 385) was impaired compared to the German population. Most patients reported problems in the dimension mobility (89.6 %), pain/discomfort (89.4 %) and usual activities (81.0 %). Except for patients with hereditary neuropathy with liability to pressure palsy (HNPP), we found no differences in HRQOL between the CMT subtypes. 72.0 % of CMT patients were satisfied with available health care services. However, patients reported to expect more CMT-specific knowledge and support as well as easier prescription and cost coverage procedures from health professionals and insurances.

*Conclusions:* The patient-reported outcomes in the assessed CMT cohort elucidate the need for more specific health care services that also address the heterogeneous phenotypes. Although the assessment has been limited to the German health services setting, insights may be applicable to CMT-specific care in other national settings.

*Keywords:* Charcot-Marie-Tooth disease, Hereditary Sensory and Motor Neuropathy, Quality of Life, Patient-Reported Outcome Measures

## VI. Research Paper #4: Cost of Illness in Inclusion Body Myositis – Results from a Cross-sectional Study in Germany

**Authors:** Senn KC, Thiele S, Kummer K, Walter MC, Nagels KH

**Published in:** Orphanet J Rare Dis. 2023;18(1):337. doi: 10.1186/s13023-023-02902-3.

**Abstract:**

*Background:* Inclusion body myositis (IBM) is the most frequent type of myositis in elder patients with a slow chronic progression and refractory to treatment. Previous cost of illness (COI) studies in IBM used claims data to estimate direct costs in the US. No evidence exists globally on both direct and indirect costs in IBM from a societal perspective. We conducted a survey in patients registered in the German IBM patient registry. Self-developed items were used to assess the utilized healthcare resources and estimate the cost. The German Self-Administered Comorbidity Questionnaire (SCQ-D), the sIBM Physical Functioning Assessment (sIFA) and patient-reported measures for satisfaction and improvements in healthcare were applied for an explorative analysis.

*Results:* In total, 82 patients completed the survey. We estimated the mean total annual per capita COI of US$102,682 (95% CI US$82,763-US$123,090) in 2021. 92.7% of the total COI were direct costs. Medical costs were similar to nonmedical costs, with substantial costs for pharmacotherapy and informal care. Depending on the prevalence estimate, the total national COI per year were US$42.7 million-US$213.7 million. Significant differences in total COI were identified for the degree of disability, marital and employment status ($p < 0.05$).

*Conclusions:* We identified remarkable and heterogenous cost in IBM. As informal care costs represented the most relevant cost driver, caregiver burden is a major factor in the patient journey. For the first time, comprehensive economic potentials were identified as a basis to improve the actual care situations and prioritizing future activities for research, pharmaceutical and digital product development as well as health politics.

*Keywords:* Cost of illness; Direct costs; Health services research; Inclusion body myositis; Indirect costs; Informal care costs; Neuromuscular disease.

## VII. Research Paper #5: A Systematic Review of Telemedicine for Neuromuscular Diseases: Components and Determinants of Practice

**Authors:** Senyel D, Senn KC, Boyd J, Nagels KH

**Submitted to:** BMC Digit Health

**Extended Abstract**

*Background:* Neuromuscular diseases (NMDs) are a heterogeneous group of mostly genetic disorders impacting muscles or peripheral nerves. They can lead to disabilities and shortened lifespans.[1, 2] Despite their severity, NMDs are still under-researched and lack in adequate therapies.[2] In general, telemedicine has been proven to be a useful tool in the treatment of chronic diseases. It has the potential to increase treatment adherence, self-management and continuity of care.[3–5] The use of telemedicine in the care of other NMDs has been rather described infrequently. An overview of the actual telemedicine usage in all NMDs has not been published. Therefore, we conducted a systematic review firstly, to summarize the status quo of telemedicine services for patients with NMDs and secondly, barriers and facilitators of the respective implementation process should be analysed.

*Methods:* The databases PubMed, Web of Science and CENTRAL by Cochrane were searched. To be truly explorative, any original evidence from any setting was included. Two independent researchers completed the screening process. Data was extracted and analysed using the taxonomy of Bashshur et al. (2011) [6] and the Consolidated Framework for Implementation Research (CFIR) [7].

*Results:* 57 original papers were included in the systematic review. The results showed a high representation of teleconsultations and remote monitoring. Teleconsultations replaced in person appointments and telemonitoring mostly focused on ventilation. Physical therapy, pulmonology, neurology, and psychology were the most represented medical specialties. Regarding the implementation process we found barriers and facilitators referring to the intervention and the individuals involved. Technical errors and inaccessibility due to a lack of technical devices or the patient's disability were stated as hindrances. The relative advantage of telemedicine over usual care was identified as the biggest benefit. A positive mindset of users as well as patient empowerment were necessary for the adoption of new technology. Technophobia or insecurity negatively impacted the implementation process.

*Discussion:* This systematic review provides an overview of the current use of telemedicine in patients with NMDs. The distribution of telemedicine interventions between the domains was very heterogenous. Previous research has neglected to describe the implementation process of telemedicine for NMDs.

*Conclusion:* The evidence shows that telemedicine can benefit patients with NMDs in a multitude of ways. Therefore, health policies should endorse and incentivize the uptake of telemedicine by institutions and health care workers. Further research needs to be conducted to confirm the current evidence and close existing research gaps.

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