Introduction
Patients with a rare disease can face treatment challenges on many different levels. The background to this thesis is therefore perhaps best exemplified with a true patient case:

A 35-year old woman residing in the Netherlands presents to the Neurology clinic with a 15-month history of sensory loss and neuropathic pain in the right leg. Electromyographic findings are consistent with chronic inflammatory demyelinating polyneuropathy (CIDP), according to international diagnostic guidelines. She is treated with intravenous immunoglobulin (IVIg), in accordance with international treatment guidelines, and her symptoms improve markedly. However, when the results of a DNA analysis are returned, they show a deletion of the PMP22 gene, changing her diagnosis to hereditary neuropathy with liability to pressure palsies (HNPP). HNPP is an autosomal dominant disorder caused by a deletion or pathogenic variant of the PMP22 gene, and is clinically characterised by repeated episodes of focal compression neuropathies, with temporary loss of function of the affected nerve and sometimes also more prolonged nerve damage. There is no curative treatment for HNPP, and management consists of supportive measures to prevent nerve compression and bracing for muscle weakness. The IVIg with which this patient had been treated until then is a human blood product produced by pooling serum IgG from thousands of healthy blood donors. Given its high production cost and limited availability, there is a large emphasis on prescribing it appropriately. HNPP is not a licensed or recommended indication for IVIg treatment and there is no sound evidence base for its use for HNPP: the only anecdotal evidence comes from a few case studies. Thus, the amended diagnosis of HNPP raises doubts about the appropriateness of continued IVIg treatment as part of evidence-based medical care. The patient’s treating physician suggests doing an n-of-one trial to determine whether she benefits from IVIg treatment for her particular signs and symptoms.

Rare diseases

HNPP is a rare disease; its prevalence is estimated to be 2 to 5 per 100,000 (see also Box 1). There are an estimated 5,000-8,000 rare diseases. Most of them are genetic in origin, but there are also rare cancers, infections, congenital malformations, and toxic and autoimmune diseases. Their prevalence varies from tens of thousands of affected patients worldwide for some rare diseases, to only a handful of families or patients for others. Despite the low prevalence for each individual rare disease, it is estimated that between 6% and 8% of the population, or between 27 and 36 million people in the EU, are affected by a rare disease because there are so many of them. This is called the “paradox of rarity”.
Box 1. Definitions of “rare”

The definition of a rare disease varies across countries and organisations. In the EU, a rare disease is defined as a disease with a maximum prevalence of 5 in 10,000 people. The US Orphan Drug Act of 1983 and the Rare Diseases Act 2002 define a disease as rare if it affects fewer than 200,000 persons in the United States (representing a prevalence of about 1 in 1,560 persons based on 2011 population figures), or if “it affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.” The global average for the prevalence criterion of the definition of a rare disease is about 40 in 100,000 persons.

For many rare diseases, treatment options are limited. Even when treatments are available, patients may have difficulty accessing these treatments due to restrictions in reimbursement. The following sections are an introduction to the healthcare regulatory landscape to understand the barriers to pharmacological treatment for rare diseases, including current approaches to overcome these barriers.

**Regulatory framework around pharmacological treatment for rare diseases**

Successful treatment of patients requires that medicines are available and accessible. Availability means that a medicine has been developed and granted marketing authorisation (MA), and that it is therefore, in principle, possible to purchase or prescribe this medicine. Accessibility means that a patient is able to obtain the medicine, usually following a prescription by a physician. Accessibility is also dependent on financial factors such as pricing and reimbursement, and other factors such as distribution of treatment.

**Availability of treatment: marketing authorisation**

The marketing authorisation procedure ensures the safety and efficacy of products on the market. During the marketing authorisation process, the benefits of the medicinal product are weighed up against its risks (the so-called ‘benefit-risk ratio’) for the indications specified in the marketing authorisation dossier. In addition, the quality of the product is scrutinised, and the summary of product characteristics (SmPC) text is defined. The SmPC text contains details of the registered indication or indications for the medicinal product (the ‘label’), clinical efficacy,

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* Non-pharmacological treatments for rare diseases, such as physical therapy, diet, and medical devices, fall outside the scope of the current thesis. Similar issues also apply to some in vitro diagnostics, but these also fall outside the scope of this dissertation.
and safety information, and forms the basis of information for healthcare professionals on how to use the medicine effectively and safely.\textsuperscript{17}

In the EU, there are several ways in which marketing authorisation for a medicinal product can be obtained: each EU member state (MS) has its own national competent authority for granting marketing authorisation, but it is also possible to apply for an EU-wide marketing authorisation via a centralised route. Marketing authorisation at a national (MS) level can be obtained by submitting a dossier for approval, or, if the medicinal product has already obtained MA in a different member state, by applying for mutual recognition of that authorisation.\textsuperscript{18} In the Netherlands, the Medicines Evaluation Board (MEB; College ter Beoordeling van Geneesmiddelen) is responsible for the assessment and marketing authorisation of medicinal products for human use, as well as their subsequent safety monitoring.\textsuperscript{19}

Apart from the national route, there is also a centralised authorisation procedure via the European Medicines Agency (EMA). For this centralised procedure, a dossier is submitted for assessment to the EMA, who advises the European Commission on whether or not to grant marketing authorisation. The centralised route is compulsory for certain medicinal products, including those designated as orphan medicinal products (OMPs) in the EU.\textsuperscript{20}

Following the adoption of the Orphan Regulation in December 1999, orphan drug designation is one of the ways in which the development and availability of treatments for rare diseases is incentivised in the EU (see Box 2 for orphan drug legislation outside the EU). Incentives include protocol assistance from the EMA, which allows the sponsor to ask what kind of studies would be needed for a marketing authorisation application; access to the centralised MA procedure; reduced fees for the MA process; 10-year market exclusivity from the time of MA; and various other incentives such as access to EU and MS research and development grants.\textsuperscript{14,21}

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**Box 2. Orphan drug legislation around the world**

The EU is not the only market that incentivises orphan drug development. In the US, the Food and Drug Administration (FDA) is tasked with the regulation of medicinal products, including marketing authorisation of orphan drugs. The US was the first country to adopt legislation to incentivise orphan drug development with the Orphan Drug Act of 1983. Incentives for orphan drug development include recommendations from the Food and Drug Administration (FDA) on the studies to be completed to register the new drug, a 50\% tax credit on clinical trials conducted in the US, a fast-track procedure for marketing approval including fee reductions, and a 7-year period of market exclusivity following market approval.\textsuperscript{22,23} The US Orphan Drug Act was followed by orphan drug legislation in Japan in 1993 and Australia in 1997.\textsuperscript{23}
*The term ‘orphan drug’ is used to describe drugs that are intended to treat diseases that are so rare that pharmaceutical companies are reluctant to develop them under normal marketing conditions because of the small sales in comparison to the cost of developing the drug.23,24

Between 2000 and 2015, the EMA approved 1,544 applications for orphan drug designation, of which 1,227 are still active (some decisions have since expired and some were withdrawn by the sponsor). To date, the European orphan drug regulation has resulted in 117 orphan medicinal products that have been granted marketing authorisation. However, these authorised products are estimated to cover just 1% of rare diseases.25 Similarly, in the US, where orphan drug policies have existed for much longer, 3,990 orphan drug designations have led to only 594 approvals for specific drug-disease combinations (as of Jan 2017).26 Thus, there seems to be a large gap between the number of drug treatments granted orphan drug designation and the number of treatments successfully brought to market.

This gap may be partly due to difficulties in obtaining the evidence needed for market approval. One contributing factor could be that a substantial proportion of treatments show disappointing effects in clinical studies despite being promising in pre-clinical studies. Another factor could be that licensing authorities, such as the EMA or the US FDA, require extensive information about drug efficacy and safety before granting market approval. Orphan drug designation does not alter the standard regulatory requirements for marketing authorisation, such as evidence of treatment efficacy and safety,27 and insufficient evidence is associated with a higher likelihood of non-approval.28 I will return to the topic of evidence after discussing the next stage of the availability-accessibility pathway: reimbursement of treatment.

Access to treatment: reimbursement

Availability of medicinal products (i.e. marketing authorisation) does not equate to access to treatment. In the EU, access to treatment is organised at a national level, with each member state deciding which treatments to include for reimbursement in the basket of healthcare services.14,29 In the Netherlands, it is compulsory for residents to obtain basic health care insurance. The Dutch National Health Care Institute (NHCI; Zorginstituut Nederland, previously College voor Zorgverzekeringen) advises the Minister of Medical Care and Sport about what should be included in the basic care package that every citizen is entitled to.30,31 The Dutch health insurance system distinguishes between medicines prescribed by medical specialists and generally used in hospital (henceforth ‘specialised medicines’) and medicines prescribed by any doctor for home use (henceforth ‘extramural medicines’). The NHCI assesses all extramural medicines and a subset of specialised medicines expected to have a high budget impact. To apply for reimbursement of a medicinal product from the basic healthcare package,
the license holder or manufacturer should submit a dossier to the NHCI. An application usually includes a pharmacotherapeutic dossier, including information about treatment efficacy and risk, a budget impact analysis and a pharmacoeconomic dossier, including cost-effectiveness and incremental cost-effectiveness ratio.\textsuperscript{30,32} For registered indications, to the extent that reimbursement is being claimed, information about the risks and benefits of treatment is taken into account.

However, medicinal products are also often used outside of the registered indication, which is referred to as ‘off-label use’ (see Box 3). Reimbursement of off-label pharmaceutical treatment is at the discretion of individual health insurance companies on a case-by-case basis, but occasionally the NHCI issues advice. Such advice can be requested by health insurance companies, healthcare providers, or patient organisations.\textsuperscript{33} For off-label use, there is usually no prior information for the particular patient population about drug efficacy and safety from clinical trials conducted by the license holder. In such cases, other evidence might be suitable for consideration. However, off-label (and indeed on-label) indications are only eligible for reimbursement when the treatment is deemed to meet the norm of ‘established medical science and practice’ (Stand van de wetenschap en praktijk).\textsuperscript{34,35}

Several types of evidence can be used to determine whether the norm of established medical science and practice is met. Professional treatment guidelines or protocols can be used as proof.\textsuperscript{35,36} In line with the current paradigm of ‘evidence-based medicine’, these guidelines or protocols tend to be based on evidence from sufficiently large, randomised controlled trials. In the absence of professional treatment guidelines, evidence from peer-reviewed studies can also be acceptable. In the past, the emphasis was on studies using a randomised controlled design, but the NHCI currently emphasises ‘fitting’ evidence in their assessment of the effectiveness of interventions.\textsuperscript{37} This ‘fitting evidence’ framework places less emphasis on the specific trial design (e.g. ‘randomised controlled trial (RCT)’), and more on which trial characteristics (e.g. ‘randomisation’) are desirable and feasible for a particular intervention in conjunction with the target population and the outcome measures. Furthermore, the evidence is assessed and graded based on quality, as per the principles of evidence-based medicine. Whenever possible, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria are used to assess the quality of the evidence.\textsuperscript{38} However, according to these criteria, evidence from RCTs is generally considered the highest level of evidence.
Box 3. Definitions of off-label use

There are several definitions of ‘off-label use’. Some define off-label use as any use of a medicine outside of its registered indication, but other definitions include as off-label use using a medicinal product in a different dose or in a different population from that for which it was registered (e.g. children instead of adults), by a different route of administration, or despite the presence of a contraindication. For the purpose of this dissertation, we define off-label use as use of a medicinal product for an indication for which it is not registered.

Evidence needed for regulatory decisions

High quality evidence of treatment efficacy and safety is therefore required for market approval and reimbursement of drug treatments. The (parallel-group) randomised controlled trial (RCT) has long been considered the gold standard of evidence for treatment benefit (efficacy). However, the rarity of rare diseases can make it difficult, or even impossible, to conduct RCTs.

In an RCT, participants are randomised to one of two (or more) parallel treatment arms, consisting of an experimental condition (or several experimental conditions) and a control condition. Treatment outcomes are then compared across these parallel groups. This type of trial usually requires large numbers of patients in each treatment arm to even out random variation between the groups of participants.

This requirement of large samples limits the usefulness of the parallel-group RCT in the case of rare diseases, where the low prevalence and geographic dispersion of patients may mean that the number of patients needed for a trial cannot be obtained, or may create substantial barriers to conducting the research in terms of funding, logistics, and ethics approval.

Over the years, many authors have suggested ways to reduce the sample size needed for clinical trials. These include using (1) continuous (rather than binary) outcome measures, (2) surrogate or composite endpoints, (3) one-sided (rather than two-sided) hypothesis testing, and (4) Bayesian analysis approaches. In addition, alternative trial designs, such as repeated measures designs, crossover trials, adaptive designs, and series of n-of-one trials, may also help to reduce the sample size needed. These approaches have therefore often been suggested for research in rare diseases. N-of-one trials may be particularly useful in reducing the sample size needed, because they combine a crossover design with repeated measures in the same patient.
N-of-one trials

N–of–one trials are double blind, multiple crossover, randomised controlled trials in a single patient.\textsuperscript{47,48} The patient undergoes multiple cycles of experimental and control treatment, and thus serves as their own control group against which to measure the effect of the experimental treatment (Figure 1), reducing the variability between treatment groups and increasing the signal–to–noise ratio. In n-of-one trials, the unit of randomisation is not the patient, but the order of the treatments over time. Block-randomisation (e.g. AB-BA-BA) is often preferred over randomisation across all planned cycles (e.g. AABBBA) so that each patient has contributed data to both treatment conditions after completion of the first cycle, allowing for a comparison across treatment conditions even in the case of early drop-out. A wash-out period between treatment periods aims to reduce carry-over effects from one treatment period to the next.

![Figure 1: Design of a single n-of-one trial (adapted and reproduced with permission from Vrinten et al., 2015.\textsuperscript{49})](image)

Suitability criteria for n-of–one trials

Due to their multiple crossover nature, n–of–one trials are suitable for symptomatic treatments for chronic, relatively stable diseases.\textsuperscript{43,47,50,51} To allow a return to baseline in the outcome measure after each treatment period, the treatment should not alter the underlying condition. In addition, the treatment should have a short onset and offset of action to reduce any carry-over effects from one treatment period to the next, and there should be a good (preferably validated) instrument to measure the outcome.\textsuperscript{43,51} N-of–one trials can be time- and resource-intensive, and the condition or the treatment should therefore be important enough to warrant setting up such a trial.\textsuperscript{42,47,50,51}

Treatment effectiveness and efficacy

By comparing the effect of the experimental with that of the control treatment across all treatment periods, an n–of–one trial can give an estimate of the effectiveness of a treatment in an individual patient. In the current paradigm of evidence-based practice, which advocates the “use of current best evidence in making decisions about the care of individual patients”,\textsuperscript{52} n–of–one trials can thus bridge the gap between treatment efficacy and treatment effectiveness.
in an individual patient (see Box 4). N-of-one trials were therefore added as highest level of evidence of treatment effects in the 2011 revision of the Oxford Centre of Evidence Based Medicine Levels of Evidence table, alongside systematic reviews of RCTs.50

**Box 4. Treatment efficacy versus treatment effectiveness**

When talking about the effects of treatment, clinicians and policymakers often distinguish treatment efficacy from treatment effectiveness. *Treatment efficacy* refers to the effects of treatment as measured under ideal conditions, such as in RCTs. RCTs often have stringent criteria regarding patient characteristics, co-morbidity, and treatment compliance, which means that results from the study population are not always generalisable to the population in which the treatment will ultimately be used. *Treatment effectiveness* refers to the effects of treatment in the (heterogeneous) population in which the medication is used in practice.53 Treatment efficacy thus focuses on the question “Can a treatment work?”, while treatment effectiveness focuses on the question “Does a treatment work?”. The discrepancy between the two is often referred to as the efficacy-effectiveness gap.54

In addition to individual treatment effects, n-of–one trials (when conducted in a series according to the same or a similar protocol) can also be aggregated to form population effect estimates.48,50,55,56 There are various ways in which data from individual n-of–one trials can be combined. For example, Zucker and colleagues compared meta-analysis models, repeated measure models, Bayesian hierarchical models, and single-period and single-pair crossover models to obtain a population comparative treatment effect of amitriptyline and fluoxetine versus amitriptyline alone on quality of life in patients with fibromyalgia.55 They concluded that the optimal model depended on the goals, data sources, and relative within- and between-patient variances. Regardless of how data are aggregated, by combining the results from individual n-of–one trials, we can simultaneously improve our medical practice for individual patients, as well as improving medical knowledge in general.48 I will briefly describe the principles of Bayesian analysis methods and how they can be applied to n-of–one trials before returning to the history and use of n-of–one trials.

**Bayesian analysis methods**

Bayesian methods are increasingly advocated for health technology assessments.57 Generally, in Bayesian analysis, information external to the study being analysed is used to define a so-called prior distribution of a parameter of interest. This prior distribution is then combined with the empirically derived data (the likelihood function) to produce an updated or posterior
distribution of the parameter of interest. Thus, in Bayesian analysis, there is explicit use of external evidence in the design, analysis, reporting and interpretation of the study results.57

Bayesian analysis methods can be used for n-of-one trials in several ways, such as to analyse data from a single n–of–one trial, to combine data from several n-of-one trials, or to test informative hypotheses. When Bayesian analysis methods are used to analyse data from a single n–of–one trial, prior knowledge, for example data from earlier observations or expert opinion (prior distribution), can be used to analyse data from the first cycle of the trial, resulting in a posterior distribution. Alternatively, data from the first cycle of the n–of–one trial can be used as the prior distribution for data analysis of the second cycle, producing a posterior distribution based on the prior distribution (data from cycle 1) and the data from cycle 2. This posterior distribution can then be used as the prior distribution for data analysis of the third cycle of the trial, and so on and so forth. This principle is called ‘Bayesian updating’.57 Using data from earlier cycles in the same n–of–one trial to inform the interpretation of the results found in subsequent cycles makes efficient use of the knowledge obtained in prior cycles of the n–of–one trial and can thus lead to a more precise estimate of the treatment effect in a single patient.

Bayesian methods can similarly be used to combine data from several n–of–one trials, except in this scenario the principle of Bayesian updating is used to integrate data from one n–of–one trial with that of the next. An example of this is the ‘Bayesian hierarchical modeling’ mentioned above.55 Using Bayesian methods in this way allows for a more precise estimate of a population treatment effect in a particular group of patients as data accumulate over time.

Bayesian analysis methods can also be an attractive alternative to frequentist methods for evaluating (informative) hypotheses.58 These are hypotheses specified using equality and inequality constraints, for example, \( H_1: \mu_1 < \mu_2 < \mu_3 \). By calculating the Bayes factor, we can also assess the strength of the evidence for this hypothesis versus an alternative hypothesis.58,59 The alternative hypothesis can be either the conventional null hypothesis (i.e. \( \mu_1 = \mu_2 = \mu_3 \)), but can also consist of an alternative hypothesis (inequality constrained or not), for example the unconstrained hypothesis “\( H_a: \mu_1, \mu_2, \mu_3 \)” which does not specify any particular relation between the three means. In Chapter 2, I will revisit the clinical case that was introduced at the start of this chapter, which uses Bayesian evaluation of inequality constrained hypotheses to analyse the data from an n–of–one trial to assess the need for continued IVIg treatment. In particular, I will assess whether IVIg infusions increase muscle strength and reduce pain more than placebo infusions and to a clinically meaningful extent, and whether there is a need for IVIg infusions every three weeks.
History and use of n-of-one trials

N-of-one trials were first described in the psychology literature in the 1960s. They became more widely known in the medical field after a series of seminal publications about their usefulness in leading medical journals in the late 1980s and early 1990s. Since then, more than 100 protocols for n-of-one trials or series of n-of-one trials have been published in the medical literature, describing trials done in more than 2,000 patients and for a variety of diseases ranging from neuropsychiatric conditions such as ADHD and psychosis, pulmonary diseases such as asthma, to the treatment of chronic pain associated with osteoarthritis, allergic syndromes, and rashes. N-of-one trials tend to be used to determine treatment effectiveness or the optimal treatment dose in an individual patient, but they can also be used to reduce ineffective prescribing and thereby reduce medical cost, repurpose existing treatments (for example, see Chapters 5 to 8), or investigate new treatments (for example, Chapter 2).

N-of-one trials are a very successful clinical tool to determine treatment effectiveness in individual patients due to the high rate of completion once started, as well as their high rate of definite answers to clinical treatment questions. For these reasons, various researchers and clinicians have tried to set up n-of-one trial services to facilitate the adoption of n-of-one trials in routine clinical practice. Guyatt and colleagues reported on their 3-year experience with one of the earliest n-of-one trial services for community and academic physicians for a range of illnesses. Out of the 70 n-of-one trials that were started using this service, 57 (81%) were completed. The most common reasons for non-completion were the patient’s non-compliance with the trial protocol or the development of a concurrent illness. In terms of trial outcomes, 48 of the 57 completed trials (84%) provided a definite clinical answer about the effectiveness of treatment. Four trials were stopped early because the trial physician observed a dramatic benefit of treatment, and two were stopped early due to perceived adverse treatment effects. In all cases, these observations were confirmed after unblinding. The high trial completion rate reported by these investigators (81%) is similar to the trial completion rate reported in a recent systematic review of n-of-one trials in more than 2,000 patients (80%). However, the review found that only 67 trials, representing 28% (N=488) of those who completed their trial, provided sufficient information in their published reports to determine change of treatment after the trial, raising important questions about how n-of-one trials are reported in the literature. Of those, a definite result was found in only 62% of patients (N=302). Table 1 presents the outcomes of the trials and the change in treatment following the trial results.
Table 1. Percentage of patients for whom n-of–one trials provided definite answers and change in treatment following the trial, as described by Gabler and colleagues (N=488).13

<table>
<thead>
<tr>
<th>Trial outcome</th>
<th>N (%)</th>
<th>Change in treatment following trial</th>
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<tbody>
<tr>
<td>Trial results favoured initial treatment</td>
<td>79 (16.2)</td>
<td>95% continued initial treatment</td>
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<tr>
<td></td>
<td></td>
<td>1% switched to alternative treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4% discontinued treatment</td>
</tr>
<tr>
<td>Trial results favoured alternative treatment</td>
<td>223 (45.7)</td>
<td>84% switched to alternative treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9% continued initial treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7% discontinued treatment</td>
</tr>
<tr>
<td>Trial results were indeterminate</td>
<td>186 (38.1)</td>
<td>49% continued initial treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35% switched to alternative treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16% discontinued treatment</td>
</tr>
</tbody>
</table>

Despite the relative success of n-of–one trials to date and the frequent suggestions that they could be used for research in rare diseases, to our knowledge, it has never been investigated whether this type of trial would be feasible and acceptable to patients, clinicians, healthcare regulators, and other stakeholders.

Research aims

The aim of this dissertation is to investigate the feasibility and clinical utility, defined as the likelihood of an improved treatment outcome, and acceptability of n-of–one trials in patients with a rare disease. The following research questions were addressed:

1. Do n-of–one trials have a role in obtaining evidence of treatment effectiveness:
   a. In a single patient with a rare disease?
   b. In a population of patients with a rare disease?

2. Are results from (series of) n-of–one trials acceptable to healthcare regulators deciding about market approval and reimbursement of treatment?

Throughout the dissertation, I use rare neuromuscular diseases as an example.

Outline of the thesis

The remaining chapters of this dissertation are structured as follows: in Part I (Chapter 2), I revisit the clinical case that was introduced at the beginning of this chapter to examine whether n-of–one trials can play a role in creating an evidence base for treatment effectiveness in a single patient with a rare disease (research question 1a). This chapter describes the results of the n-of–one trial that was specifically designed for this patient’s case, and which aimed to formally assess the effectiveness of IVIg treatment to justify her continued use of it. The n-of–one trial uses an adaptation of the classical n-of–one trial design: one with a “rescue” option one week after each randomised trial infusion. Bayesian evaluation of informative hypotheses...
was used to examine whether infusions of IVIg every three weeks were superior to placebo in alleviating muscle pain and weakness.

**Part II** (Chapter 3) examines the hypothetical views of various stakeholders on n–of–one trials for rare diseases before implementation of such trials. I identified four groups of stakeholders: pharmaceutical industry, healthcare regulation and policy, clinical and academic research, and patients and consumers. Their views on n–of–one trials for rare diseases were elicited during a multidisciplinary stakeholder meeting. The clinical case presented in Chapter 2 was also presented during this meeting to illustrate how n-of-one trials can be used to obtain evidence of treatment effectiveness in patients with a rare disease. The qualitative analysis of this meeting most importantly showed that regulatory decisions are made for populations of patients, not for individual patients. This finding helped shape an answer to research question 2 and also helped to shape the remainder of this dissertation.

Based on the findings of the stakeholder meeting, I helped design a pilot implementation of a series of n-of–one trials to inform regulatory decisions, which is described in **Part III** (Chapters 4 to 7). These chapters focus on the question whether n-of–one trials can be used to determine treatment effectiveness in a population of patients with a rare disease (research question 1b). We decided to focus on ephedrine for the treatment of the rare neuromuscular disease myasthenia gravis as the topic of our study, after conducting a survey among 3,532 members of the Dutch Neuromuscular Diseases Association (Spierziekten Nederland) in February 2011, asking them which medicines they were taking for their neuromuscular disease that were not (or no longer) reimbursed by their health insurance companies. In total, we received 229 completed questionnaires and 60 emails from patients, listing 134 drug-disease combinations. We also surveyed neuromuscular disease specialists in the Netherlands via the Dutch platform for neuromuscular disease specialists and researchers (formerly “Interuniversitair Steunpunt Neuromusculair Onderzoek”, now called “Spierziekten Centrum Nederland”, Dutch Neuromuscular Centre), who listed 15 drug-disease combinations. We then collated these lists and compared them with the criteria described above to see which combinations fulfilled the suitability criteria of n-of–one trials.

Three suitable drug-disease combinations were identified: mexiletine for non-dystrophic myotonia, 3,4-diaminopyridine for myasthenia gravis, and ephedrine for myasthenia gravis. The first of these was already being investigated by another research team from the Netherlands.\(^6\) The drug of the second drug-disease combination had recently become the focal point of some controversy.\(^6\) We therefore decided to focus on the third drug-disease combination: ephedrine for myasthenia gravis. The oral (tablet) form of ephedrine had already been granted marketing authorisation in Spain for the treatment of asthma.\(^7\) We investigated whether it could be repurposed for the treatment of myasthenia gravis.

Chapter 4 presents the results of a Cochrane systematic review of ephedrine for the treatment of myasthenia gravis, neonatal myasthenia, and the congenital myasthenic syndromes, which
shows that despite its widespread use, there is very little high quality evidence to support it. Chapter 5 describes the study protocol for a series of placebo-controlled, double blind n-of-one trials to assess the effect of add-on ephedrine for autoimmune myasthenia gravis. Chapter 6 presents the findings of this small series of n-of-one trials, while Chapter 7 describes the findings from the optional 6-month open-label extension phase of the series of n–of–one trials.

Apart from the clinical outcome measures, we also qualitatively evaluated the feasibility and acceptability of this type of trial to patients and trialists. We proceeded to ask the Medicines Evaluation Board and the Dutch National Health Care Institute, who decide about marketing authorisation and reimbursement of treatment in the Netherlands, respectively, to provide scientific advice on the feasibility of using the evidence obtained in the series of n-of–one trials for regulatory decisions. Part IV (Chapter 8) presents the perspectives of patients, trialists, and the two regulatory stakeholders, and provides a more empirical answer to the question whether results from n–of–one trials are acceptable to healthcare regulators (research question 2).

Finally, Part V presents a discussion of our findings (Chapter 9), and a summary of this dissertation (Chapter 10). Table 2 presents the main research questions for each chapter of the thesis.
Table 2. Research questions per part and chapter of dissertation

<table>
<thead>
<tr>
<th>Part/Chapter</th>
<th>Research questions</th>
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<tbody>
<tr>
<td>Part I</td>
<td>Do n–of–one trials have a role in obtaining evidence of treatment effectiveness in a single patient with a rare disease?</td>
</tr>
<tr>
<td>Chapter 2</td>
<td>Are IVIg infusions every three weeks superior to placebo in alleviating muscle weakness and pain in this patient with a hereditary neuropathy?</td>
</tr>
<tr>
<td>Part II</td>
<td>Are results from (series of) n-of-one trials acceptable to healthcare regulators deciding about market approval and reimbursement of treatment?</td>
</tr>
<tr>
<td>Chapter 3</td>
<td>What are the views of stakeholders on using results from series of n-of-one trials to decide about market approval and reimbursement of treatment for populations of patients with a rare disease?</td>
</tr>
<tr>
<td>Part III</td>
<td>Do n-of-one trials have a role in obtaining evidence of treatment effectiveness in a population of patients with a rare disease?</td>
</tr>
<tr>
<td>Chapter 4</td>
<td>What is the current evidence for ephedrine in the treatment of myasthenia gravis?</td>
</tr>
<tr>
<td>Chapter 5</td>
<td>A research protocol for a small series of n-of-one trials for add-on treatment with ephedrine for myasthenia gravis</td>
</tr>
<tr>
<td>Chapter 6</td>
<td>What is the short-term effect and safety of add-on treatment with ephedrine for patients with myasthenia gravis who do not sufficiently respond to standard treatment?</td>
</tr>
<tr>
<td>Chapter 7</td>
<td>What is the 6-month effect of add-on treatment with ephedrine for patients with myasthenia gravis who do not sufficiently respond to standard treatment?</td>
</tr>
<tr>
<td>Part IV</td>
<td>Are results from (series of) n-of-one trials acceptable to healthcare regulators deciding about market approval and reimbursement of treatment? (continued)</td>
</tr>
<tr>
<td>Chapter 8</td>
<td>Is it feasible to conduct a series of n-of-one trials for a rare disease, and what is the utility of the results for regulatory decisions?</td>
</tr>
<tr>
<td>Part V</td>
<td>Discussion</td>
</tr>
<tr>
<td>Chapter 9</td>
<td>Implications of the studies’ findings, remaining questions and directions for future research</td>
</tr>
</tbody>
</table>
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