PART V

Discussion and summary
Discussion
BACKGROUND AND OBJECTIVES

Worldwide incentives aim to accelerate the development of treatments for rare diseases. Availability and accessibility to treatment may be hindered, however, by the evidence needed for regulatory decisions, which tend to require high quality evidence of treatment efficacy and safety from large randomised controlled trials. Financial, logistical, time and geographical barriers may prevent such trials from being conducted in populations of patients with a rare disease, and the relatively small numbers of patients available for research may further limit the feasibility of obtaining the appropriate evidence. To overcome these barriers, various alternatives have been proposed, including alternative trial designs such as n-of-one trials.\textsuperscript{1-3}

To our knowledge, hardly any research had been done to examine whether this type of trial would be feasible and acceptable to patients with a rare disease, the clinicians who treat them, the healthcare regulators who decide on market approval and reimbursement, and other stakeholders.

The aim of this dissertation was therefore to investigate the feasibility, clinical utility, and acceptability to various stakeholders of n-of-one trials in patients with a rare disease. Specifically, we examined whether n-of-one trials have a role in obtaining evidence of treatment effectiveness in a single patient with a rare disease as well as in a population of patients with a rare disease, and whether results from n-of-one trials would be acceptable to healthcare regulators deciding about market approval and reimbursement of treatment, using rare neuromuscular diseases as an example.

In this general discussion, the main findings will be briefly summarised, followed by a reflection on these findings. This is followed by a discussion of the implications for practice, suggestions for future research, and the overall conclusions of the dissertation.

MAIN FINDINGS

N-of-one trials to examine treatment effectiveness in a single patient with a rare disease

Over the past decades, numerous authors have used n-of-one trials to examine treatment effectiveness with the aim of optimising individual patient care for a myriad of diseases.\textsuperscript{4-6} Various authors have suggested that n-of-one trials could also be used to obtain evidence of treatment effectiveness in patients with a rare disease,\textsuperscript{1-3} but to our knowledge these suggestions had never been put to the test in practice. In Chapter 2, we demonstrated that it is feasible to set up an n-of-one trial for a single patient with a rare disease in regular clinical practice. Our trial also provided evidence of clinical utility: our patient responded better to treatment than to placebo on both outcome measures and her improvements were both statistically significant and clinically meaningful. We were thus able to justify her continued use
of an expensive, long-term treatment that would otherwise not have been indicated for her disease according to current diagnostic and treatment guidelines.

**N-of-one trials to examine treatment effectiveness in a population of patients with a rare disease**

Although Chapter 2 provided an example that n-of-one trials can be used to determine treatment effectiveness in individual patients with a rare disease, the real potential of n-of-one trials is to provide accumulating evidence of treatment effectiveness in a population of patients with a rare disease. In Chapters 4, 5, 6, and 7, we piloted a small series of trials, using ephedrine for myasthenia gravis as a proof-of-principle example.

In our literature review in Chapter 4, we showed that despite the sporadic use of ephedrine in clinical practice, no randomised controlled trials have been conducted to examine its effectiveness in myasthenia gravis. Evidence from five case reports suggested a beneficial effect on muscle strength, endurance, and overall myasthenic symptoms, although some patients also experienced adverse effects.

The small series of n-of-one trials that we set up (Chapter 5) were block-randomised, double-blind, placebo-controlled trials with three crossover treatment periods to examine the effect of add-on therapy with ephedrine on the Quantitative Myasthenia Gravis (QMG) score (a validated scale ranging from 0 to 39 to assess muscle strength and fatigability in myasthenia gravis). Pooling of the results of 4 completed n-of-one trials (Chapter 6) showed that ephedrine improved the QMG score by 1.0 point (95% CI 0.21-1.79). This was significant for the group of patients included in the trials, but also when inferred to the population effect. Some adverse effects were reported, such as palpitations and restlessness, but these were mild and transient.

In addition to the short-term effect of ephedrine, we also examined its effect over the longer term in an open-label extension phase (Chapter 7; we shall refer to the series of n-of-one trials and the open-label extension phase together as “the trial”). This showed that the beneficial effect of ephedrine was not maintained during 6 months of follow-up, with no significant differences in QMG scores over the 6-month follow-up compared with baseline scores.

Trialists’ experiences were also evaluated (Chapter 8). Although the trial was relatively easy to conduct due to the simple nature of the intervention, the small number of patients and the trial’s short duration, the clinicians and hospital pharmacist spent more time on it than anticipated. For the clinicians, this was due to delays in getting the required ethical approval and in finding patients who met the inclusion criteria of the trial, while the poor availability of the trial medication led to additional administrative duties to import the medication for the hospital pharmacist. In addition, considerable funding was necessary to lay the groundwork for and to conduct the trial.
We also evaluated the experience of patients. Our pre-specified quantitative criterion for trial feasibility was met, with all four patients completing all three treatment cycles. Patient interviews conducted after the n-of-one trials showed that patients felt well-informed about the trial, were positive about its utility, which was expressed both in terms of personal benefit and scientific progress, appreciated learning their individual trial results to guide their future therapy and were generally happy with the time investment needed for the trial. They appreciated the flexibility to have breaks during the trial. They also suggested several ways in which future n-of-one trials could be improved, including arranging for the clinical measurements to be done in a nearby clinic, administering the self-reported side effects questionnaire more regularly, and considering not scheduling different participants’ trial visits back-to-back to avoid patients being confronted with each other’s on-going trials.

From this proof-of-principle trial, we can conclude that series of n-of-one trials can also be successfully used to obtain evidence of treatment effectiveness in a population of patients with a rare disease. As with our patient presented in Chapter 2, however, clinical utility for this group would also depend on continued availability and access to treatment. This depends in turn on whether healthcare regulators make a favourable decision regarding the provision of this treatment for this patient population, which leads to the next research question.

Acceptability of evidence from (series of) n-of-one trials to healthcare regulators

We evaluated the acceptability of evidence from n-of-one trials to healthcare regulators in two ways. First, we convened a multidisciplinary stakeholder meeting including representatives from healthcare regulation and policy to elicit their views on using (series of) n-of-one trials for decisions about market approval and reimbursement of treatments for rare diseases (Chapter 3). The results of this meeting informed the design of the clinical trial described in Chapters 4 to 7. We then asked the Dutch regulatory organisations deciding about market approval (Medicines Evaluation Board, MEB) and reimbursement via the Dutch uniform healthcare package (National Health Care Institute, NHCI) for scientific advice on whether the results of our trial could be used to inform regulatory decisions.

Regulators acknowledged that their current frameworks, which emphasise evidence from large, randomised controlled trials, are not suited to populations of patients with a rare disease. In principle, they would be willing to consider aggregated evidence from a series of n-of-one trials, although the MEB stated that this would have to be a last resort option and that treatment safety would have to be substantiated in some other way. Both organisations underlined the importance of meeting the suitability criteria for n-of-one trials as set out by Nikles and colleagues\(^7\) and Nikles and Mitchell.\(^8\)

When presented with the results from our series of n-of-one trials, neither organisation felt that the evidence was sufficient to inform a regulatory decision on licensing or reimbursement of ephedrine as add-on therapy for myasthenia gravis, although the NHCI did state that evidence

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from the n-of-1 trial design fits their “Feasible Information Trajectory”\(^9\). The representativeness of the study sample (and thus the generalisability of the findings), the clinical significance of the (statistically significant) results, and the variability of individual responses to treatment were all questioned. Neither organisation could comment on how many more patients should be included in such a series of n-of-one trials to improve generalisability. In addition, the MEB questioned whether the suitability criteria for n-of-one trials had been met in this case, and suggested using a different study design, such as a parallel group trial.

**REFLECTION ON MAIN FINDINGS AND STUDY METHODS**

This section provides a reflection on the main findings and study methods for each of the three research questions separately.

**N-of-one trials to examine treatment effectiveness in a single patient with a rare disease**

In Chapter 2, we showed how an n-of-one trial may provide evidence of treatment effectiveness in a single patient with a rare disease. This trial is important for several reasons. First, from a clinical neurology perspective, it provides further evidence that some patients with a hereditary neuropathy may benefit from anti-inflammatory treatment, and may thus support previous observations from case studies that hereditary and inflammatory neuropathies may co-occur (e.g. \(^{10,11}\)).

Furthermore, from a methodological perspective, the strength of the evidence for treatment benefit derived from this study is greater than that provided by previous case reports. According to the Oxford Centre for Evidence Based Medicine, n-of-one trials, alongside systematic reviews of randomised trials, are considered the highest level of evidence of treatment benefits and harms (Level 1).\(^2\) This reflects the fact that n-of-one trials are uniquely positioned to provide evidence of treatment effectiveness for an individual patient, while randomised controlled trials can only provide evidence of average treatment effect in a population of patients.\(^3\) This reflects one of the two purposes of n-of-one trials that were identified during our stakeholder meeting (Chapter 3).

Providing evidence of treatment effect in an individual patient may pave the way for personalised, evidence-based medicine and may be especially important for some of the ultra-rare diseases where it may prove difficult to aggregate data from multiple patients. In our example, data from the n-of-one trial were used to justify continuing chronic treatment with an expensive drug. We shall return to the topic of n-of-one trials for reimbursement purposes in more detail when we reflect on the final research question.
In addition to tailoring treatment to patients, this example also shows how the design of an n-of-one trial can be tailored to the needs of the individual patient.\textsuperscript{14} The scientific yet patient-centred approach of an n-of-one trial may help empower patients and enhance shared decision making in the doctor-patient relationship.\textsuperscript{13,15,16} For example, in this trial, subjective outcome measures that were important to the patient were used. The classic block-randomised design of the n-of-one trial was also adapted to include a rescue option to make the trial more acceptable to the patient by ensuring that an effective treatment would not be withheld for too long. These features may increase the acceptability and applicability of n-of-one trials to patients, but may also make aggregating data from different patients more difficult.

This study also demonstrates the use of Bayesian analysis methods in n-of-one trials. We used Bayesian evaluation of informative hypotheses, which allowed us to evaluate hypotheses that could not be evaluated with standard frequentist methods; for example, the combined hypothesis that the treatment was better than placebo and that the difference was clinically meaningful. Bayesian methods can also be used in other ways to analyse data from n-of-one trials, such as in Bayesian updating, whereby results from a previous trial inform the analyses of the next trial.\textsuperscript{14,17} This particular use of Bayesian analysis may be especially informative when data are accumulated over time. By using informative priors, trials can borrow strength from previous research findings. An example of a series of n-of-one trials for a rare disease that uses Bayesian analysis with informative priors is the on-going trial of mexiletine for non-myotonic dystrophia by Stunnenberg and colleagues.\textsuperscript{18} The use of Bayesian updating in the analysis of n-of-one trials was beyond the scope of the current dissertation, although the n-of-one study findings presented here could be used to inform the prior expectations for similar future studies if Bayesian analysis were used.

Possible limitations to the use of n-of-one trials to examine treatment effectiveness in individual patients with a rare disease include the general conditions for suitability of n-of-one trials, such as that the disease has to be relatively stable, the treatment must be symptomatic (i.e. a return to baseline should be possible), the on- and off-set of the biological action of the treatment must be relatively fast to allow multiple crossovers, and there must be a valid and reliable method to measure the outcome or surrogate outcome.\textsuperscript{7,8} As described in the Introduction, we conducted surveys among members of the Dutch Neuromuscular Diseases Association and neuromuscular disease specialists in tertiary medical centres in the Netherlands to investigate for which medicine-neuromuscular disease combinations reimbursement problems existed. Despite the large number of responses, only three treatment-disease combinations were suitable for n-of-one trials. This suggests that, at least where rare neuromuscular diseases are concerned, n-of-one trials are only part of the solution, and this may negatively affect the relative priority of implementing n-of-one trials for rare diseases over other types of trial design.
N-of-one trials to examine treatment effectiveness in a population of patients with a rare disease

Chapters 4 to 8 demonstrated that series of n-of-one trials can be successfully conducted in a population of patients with a rare disease, and that the results from such a series can be pooled to obtain a population effect estimate. Several observations can be made about the results of this clinical study.

First, there are various analytic methods to combine results from n-of-one trials to produce a population effect estimate and it is unknown which is the best one. Zucker, Ruthazer, and Schmid\(^{19}\) compared summary and individual patient data meta-analysis, Bayesian hierarchical models, repeated measures analysis, and crossover analysis models and concluded that the selection of model will depend on the goals, data sources, and relative within- and between-subject variances. In our study, we used a linear model with fixed effects for treatment and patient to determine the overall treatment effect within the population of trial participants, then added a random treatment effect to infer to the population level as prespecified in case the trial treatment effect would be statistically significant. It is also currently unknown how such aggregated n-of-one population effect estimates would compare to results obtained with a gold-standard parallel-group randomised controlled trial, although the first comparative trials are currently underway.\(^{18,20}\)

Secondly, although our series of n-of-one trials was successful in terms of demonstrating feasibility and clinical utility of n-of-one trials in a population of patients with a rare disease, several barriers to more widespread implementation were noted, such as time and financial constraints. These concerns were also expressed during our multidisciplinary stakeholder meeting before we set up our trial (Chapter 3) and have been expressed previously in the context of n-of-one trials for other diseases.\(^{13,21,22}\) For example, in a qualitative vignette study exploring potential barriers and facilitators of n-of-one trials among physicians and patients with a chronic illness, Kravitz and colleagues noted that “n-of-one trials require effort both cross-sectionally (during a single visit) and longitudinally (across an episode of care)”.\(^{13}\) Both doctors and patients in their study commented that the increased time demand on doctors may be a barrier to widespread implementation. Interestingly, doctors in this study also expected their patients to be put off n-of-one trials by the time demand, but this concern was not echoed by patients. In our study, trial participants found the time investment considerable, but nonetheless all four completed the entire n-of-one trial. Their motivation may partly be due to the personal benefit they expected to derive from the trial, as well as more altruistic motives such as the advancement of science for this rare disease. We will discuss financial constraints as a barrier to widespread implementation of n-of-one trials below.
Acceptability of evidence from (series of) n-of-one trials to healthcare regulators

Neither the MEB nor the NHCI felt that the evidence presented in our clinical study would have been sufficient to make a decision about market approval or reimbursement. Main sticking points were the generalisability of the study findings and whether the demonstrated effect was clinically relevant.

In rare disease research, the question of generalisability can be a tricky one; it depends on several factors, including the fidelity of the implementation of the study intervention in real-world settings, but also on how well the study sample represents the population of patients with that disease. Regulators questioned how representative our study sample of 4 patients with myasthenia gravis (MG) was. Given that the estimated prevalence of MG is 155-180 per million in the Netherlands,\textsuperscript{23} and there are therefore an estimated 2500-3000 MG patients in the Netherlands alone, this critique may seem justified. (Although note that many patients can be managed well with first line treatment and would therefore not have met the inclusion criteria of our proof-of-principle trial.) However, for even rarer diseases, a sample size of 4 patients may well be all that is achievable. Generalisability should therefore not just be judged on the absolute number of patients included in a series of n-of-one trials, but also on the number of patients included in the series relative to the total number of patients with the disease and the disease characteristics that determine appropriateness of the intervention.

In addition, the debate about generalisability may also be meaningfully informed by comparing between- and within-person variances. A simulation study by Zucker and colleagues\textsuperscript{19} shows that precision of the effect estimate increases with larger numbers of patients included in a series of n-of-one trials and with more crossover pairs per n-of-one trial. However, the number of patients and the number of pairs were not of equal importance: when the between-patient variance was small compared with the within-patient variance, additional measurements on each patient increased precision much more than additional patients. On the other hand, when within-patient variance was small compared with between-patient variance, additional measurements per patient were of less value than recruiting additional patients into the trial.\textsuperscript{19}

The question of clinical utility of the study findings was also raised, as regulators questioned whether an average 1.0-point improvement on a 39-point scale could be considered clinically meaningful. Despite the MEB and NHCI’s mandate to make decisions for populations of patients, not individual patients, they asked to see the individual patient data to determine if individual patients could be classed as ‘responders’. In this project, we tried to stay as close as possible to the current regulatory frameworks, by presenting aggregated data for our sample and by using n-of-one trials that feature aspects of the gold-standard randomised controlled trial, such as randomisation and blinding (while also working within the constraints of the rare disease population). However, in the era of precision medicine, not only of diagnosis but also of treatment, this mandate may be changing. For example, treatments tailored to the genetics
of an individual may mean that market approval and reimbursement decisions are no longer exclusively made for groups of patients, but may also need to be made for “n=1”. Defining clinical utility then will require closer debate about what counts as evidence of responsiveness to treatment: an average effect for a group of patients, or an effect in individual patients? The request from the MEB to see the individual patient data for our series of n-of-one trials may reflect this shift from group-level to individual-level data. N-of-one trials, which can provide both types of data, may thus be a confusing hybrid that raises more questions than it answers. As Kravitz and colleagues\(^22\) noted: “The dual nature of n-of-one trials (incorporating research and clinical care) can challenge the most acute intelligence […]”. It is important that there is agreement between stakeholders about what counts as clinical utility in the regulatory appraisal process and how individual utility versus group-utility is dealt with. This may also affect the requirements for informed consent from prospective n-of-one trial participants, for example, if a negative result at the group-level could negatively affect availability or accessibility of the treatment for those n-of-one trial participants who showed a positive response to treatment.

External policy factors may provide an impetus for regulators to take note of n-of-one trials. As mentioned before, n-of-one trials have often been hailed as a research method for rare diseases,\(^1,2\) not least of all by healthcare regulators themselves.\(^3,24\) Following the EU Council Recommendation on an action in the field of rare diseases, all EU member states have committed themselves to developing a national plan for rare diseases, outlining how current research activities into rare diseases, expertise centres and European Reference Networks, and patient organisations for rare diseases can be facilitated and fostered.\(^25\) One of the aims of the Dutch national plan is to stimulate scientific research into the treatment of rare diseases,\(^26,27\) and n-of-one trials could contribute to this.

Another external factor that may encourage the acceptance of evidence from n-of-one trials is the rise of personalised medicine and targeted and tailored treatments. As Kravitz and colleagues put it: “N-of-one trials require substantial time, effort, and resources. Still, it is reasonable to wonder why society is willing to invest billions of dollars for technology that helps us get the right diagnosis but has not embraced an approach that can dramatically increase the likelihood that a patient gets the right treatment” (p.541).\(^22\) With the advent of new and often expensive biologicals and increased pressure on healthcare budgets, healthcare regulators and purchasers are encouraged to allocate therapies to those most likely to benefit. This does not necessarily mean that regulators need to accept evidence from n-of-one trials, but these developments may favour a regulatory climate in which evidence from n-of-one trials may be one of the new types of evidence that they would be willing to consider. Performance-based reimbursement schemes that link reimbursement to health outcomes, such as coverage with evidence development, conditional treatment continuation or performance-linked reimbursement schemes,\(^28\) may be instrumental in making personalised or stratified decisions
about reimbursement of treatment. These types of schemes may be more difficult to realise for decisions about market approval, for which evidence of treatment safety would also need to be substantiated, although some countries have indeed implemented such schemes, or are exploring their implementation.

**IMPLICATIONS FOR PRACTICE**

N-of-one trials for rare diseases can be used in several ways. As demonstrated in Chapter 2, n-of-one trials can be a useful tool to determine treatment effectiveness in individual patients for chronic, symptomatic treatments with a short on- and offset of action. Because of the effort involved in setting up and running an n-of-one trial, it is particularly suited to treatments where the effect of treatment is variable or uncertain, such as for many symptomatic treatments for rare diseases that are currently being prescribed off-label. In these cases, an n-of-one trial may provide the necessary evidence to put in a motivated request for reimbursement with the patient’s health insurance provider, if reimbursement is uncertain or denied.

N-of-one trials may also have a role to play in treatment guidelines. For example, our series of n-of-one trials of ephedrine for myasthenia gravis showed that while some patients benefitted from add-on treatment with ephedrine, for others the treatment effect did not outweigh the adverse effects. Treatment guidelines for rare diseases could incorporate n-of-one trials to determine the best treatment for individual patients, rather than a “one-size-fits-all” approach to treatment. Previous research in more common conditions has shown that n-of-one trials can result in more cost-effective prescribing in the long term. Using n-of-one trials to determine which patients benefit from certain treatments may thus help to contain costs, given the rise of innovative but often expensive new therapies for rare diseases, such as biologicals.

**RECOMMENDATIONS FOR FURTHER RESEARCH**

Originally, the aim of the project that formed the basis for this dissertation was to examine the necessary preconditions for an n-of-one trial service for rare diseases, but we quickly discovered that the need for such a service was not immediately apparent to some stakeholders, and that the value or utility of n-of-one trials themselves needed further exploration before n-of-one trials (or an n-of-one trial service) could be widely implemented for rare diseases. Various authors have explored the enthusiasm for n-of-one trials as a tool to improve therapeutic precision among clinicians, patients, and other stakeholders. Over the course of our research, we encountered many of the same barriers to wider implementation of n-of-one trials. These include the cost and time investment involved in the setting up and running of the trials, and the leadership needed to drive n-of-one trials for rare diseases forward.
Who will pay for n-of-one trials?
The costs associated with an intervention can negatively impact its implementation, and the question of who should pay for n-of-one trials, or an n-of-one trial service, is therefore an important one. Like most other series of n-of-one trials to date, our clinical study was paid for by research funds. But alternative funding sources are conceivable, because n-of-one trials for rare diseases could be implemented in many different settings. For example, the pharmaceutical industry may be interested in sponsoring series of n-of-one trials, if they can serve as a vehicle for licensing treatments for smaller patient populations, including drug repurposing. Alternatively, n-of-one trials could be paid for out of health insurance premiums when pay-for-performance models are used. Thus, the question of who should pay for n-of-one trials can be rephrased as a question about who – on a societal level - benefits from the evidence that such trials provide, and therefore who would be willing to adopt a championing role for series of n-of-one trials for rare diseases.

Who will drive n-of-one trials for rare diseases forward?
The answer to the question of who should champion n-of-one trials is not a straightforward one. Ultimately, patients with a rare disease reap the benefit of these trials, potentially both as individuals and as a group. But as discussed in Chapter 3, the time and expertise needed to successfully carry out these trials is probably too much for individual patients or even patient organisations. Clinicians who treat patients with a rare disease may be an obvious alternative choice, but are often already inundated with clinical work to take on a championing role. Previously, n-of-one trial services for more common illnesses, catering to the need of patients and clinicians while minimising the effort involved on the part of clinicians, have been set up by academic researchers. Some of these trial services have been directly marketed to patients, and have been fairly successful. However, as mentioned before, these trial services were mostly paid for out of research funds, and ceased to exist when research funds dried up and/or other research opportunities beckoned. Although n-of-one trials can encourage rational prescribing and thereby reduce healthcare costs, Chapters 3 and 8 seem to suggest that healthcare regulators feel that their role is only to appraise the evidence obtained from (series of) n-of-one trials when presented to them, not to actively promote this type of trial. Pharmaceutical companies, who, as mentioned before, may benefit from using n-of-one trials as a means of licensing treatments for small populations, may be put off by the continued uncertainty around the acceptability of evidence obtained in these trials to healthcare regulators. In addition, there may not be an incentive for pharmaceutical companies to license medications that are already used off-label, even if evidence of treatment effectiveness could be proven by means of series of n-of-one trials. Another stakeholder who may stand to benefit from a wider implementation of n-of-one trials for treatments for rare diseases are
health insurance companies, where treatments are already used off-label. Despite efforts to invite the views of this stakeholder during the multidisciplinary stakeholder meeting (Chapter 3), their views remain underrepresented in this dissertation. More research into the attitudes of health insurance companies towards n-of-one trials for rare diseases, and the feasibility of implementing them within their current legal and ethical frameworks, may be warranted. The push to put rare diseases on the national research agenda has been a collaborative effort between many stakeholders (e.g. 26). Similarly, establishing n-of-one trials as a research and clinical care tool for rare diseases may require collaboration between multiple stakeholders, for example, in clinical research networks or expert centres.22 However, as long as the relative advantage, i.e. the perception of the advantage of implementing this intervention vs. another one,25 cannot be made clear to stakeholders, n-of-one trials will never take off. Thus, a suitable “business case” for n-of-one trials for rare diseases needs to be further developed.22

As part of the development of a suitable business case for n-of-one trials, the possibility of an n-of-one trial service and/or n-of-one trial registry and database for rare diseases could be explored. An n-of-one trial service could provide the necessary expertise to design and conduct individual n-of-one trials, and could assist with tasks such as preparing the study medication, providing data collection instruments, and analysing and reporting on the results of the trials; thus lessening the burden on clinicians. A registry and/or database of n-of-one trials for rare diseases could help to conduct n-of-one trials according to the same research protocol across multiple study sites, even internationally, and could facilitate aggregating data from individual n-of-one trials to obtain population effect estimates. The recently published CONSORT Extension for reporting of N-of-1 Trials (CENT) guidelines37, 38 could help to determine the kind of data to be recorded in such a database. However, issues around data controlling and processing, and publication rights may warrant further investigation before such registries or databases are set up.

CONCLUSIONS

N-of-one trials can provide evidence of treatment effectiveness in patients with a rare disease. When conducted according to the same protocol, results from series of n-of-one trials can be aggregated to allow estimation of the population effect of an intervention, which could serve as the basis for regulatory decisions about market approval and reimbursement of treatment. The scope for n-of-one trials is limited, however, to symptomatic treatments with a fast onset and offset of action for relatively stable diseases. Furthermore, for regulatory decisions, generalisability of the evidence from n-of-one trials, as well as treatment safety, would also need to be substantiated. Within these limitations, n-of-one trials are a useful tool to bring rational pharmacotherapy to patients with a rare disease, and their structural implementation in healthcare systems and/or rare disease research warrants further consideration and investigation.
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