IQWiG Reports – No. A20-61

Concept for a routine practice data collection according to the Law for More Safety in the Supply of Medicines (GSAV) – onasemnogene abeparvovec[1]

Rapid Report

[1] Translation of the rapid report A20-61 *Konzept für eine anwendungsbegleitende Datenerhebung – Onasemnogen-Abeparvovec* (Version 1.0; Status: 1 October 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Concept for a routine practice data collection according to the Law for More Safety in the Supply of Medicines (GSAV) – onasemnogene abeparvovec

Commissioning agency
Federal Joint Committee

Commission award on
16 July 2020

Internal Commission No.
A20-61

Name of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln

Tel.: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

This report was prepared without the involvement of external experts.

IQWiG employees

- Sascha Abbas
- Ralf Bender
- Raphaela Gorris
- Thomas Kaiser
- Ulrike Lampert
- Jörg Lauterberg
- Ulrike Mikulić
- Beate Wieseler

Keywords: Onasemnogene Abeparvovec, Muscular Atrophy – Spinal, Registries, Benefit Assessment, Concept

Table of contents

Page

Table of contents ..... **v**
List of abbreviations ..... **vi**
Preliminary note ..... **vii**
1 Background **1**
2 Research question of the report **2**
3 Course of the project **3**
4 Methods **4**
5 Results 5
5.1 Need for information for the benefit assessment of onasemnogene abeparvovec **5**
5.2 Research question of the RPDC-GSAV **5**
5.3 Data sources available **7**
5.3.1 Ongoing and planned data collections on onasemnogene abeparvovec from requirements of regulatory and other approval authorities 8
5.3.2 Registries as a potential data source for the RPDC-GSAV 18
5.3.2.1 Result of the search for disease registries 18
5.3.2.2 Registry characteristics 20
5.3.2.3 Evaluation of the suitability of the registries identified as a data source for an RPDC-GSAV for benefit assessments according to §35a SGB V 21
5.3.2.3.1 Information sources to evaluate the suitability of registries 21
5.3.2.3.2 Suitability evaluation, taking into account nationally and internationally used quality criteria for registries 22
5.4 RPDC-GSAV according to §35a (3b) SGB V **27**
5.4.1 Type of RPDC-GSAV 27
5.4.1.1 Study design of RPDC-GSAV 27
5.4.1.2 Data sources for the RPDC-GSAV 30
5.4.2 Duration and scope of the RPDC-GSAV 32
5.4.3 Data analysis 35
6 Discussion **39**
7 Conclusion **41**
References 43
Appendix A Search strategies for searches in bibliographic databases **49**
Appendix B Responses from registry operators **50**
B.1 Response from the RESTORE registry **50**

B.2 Response from the SMArtCARE registry 51
B.3 Response from the TREAT-NMD SMA global registry..... 61
Appendix C Fulfilment of nationally and internationally used quality criteria by the identified registries 72
Appendix D Studies on nusinersen 75

Table of contents

Page

Table 1: PICO patient group A for the RPDC-GSAV xii
Table 2: PICO patient group B for the RPDC-GSAV xiii
Table 3: PICO patient group A for the RPDC-GSAV 6
Table 4: PICO patient group B for the RPDC-GSAV 7
Table 5: Characteristics of the data collections designated by EMA and FDA 10
Table 6: Assignment of data collections to onasemnogene abeparvovec (interventional 1-arm studies) 17
Table 7: Results of the search for disease registries 19
Table 8: Assignment of available nusinersen study arms to relevant patient groups. 29
Table 9: PICO patient group A for the RPDC-GSAV 41
Table 10: PICO patient group B for the RPDC-GSAV 42
Table 11: Characteristics of studies on nusinersen 75

List of abbreviations

Abbreviation	Meaning
BSC	best supportive care
CI	confidence interval
EMA	European Medicines Agency
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GSAV	Gesetz für mehr Sicherheit in der Arzneimittelversorgung (Law for More Safety in the Supply of Medicines)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PICO	patient/population, intervention, comparison, outcomes
RPDC-GSAV	routine practice data collection according to the GSAV
SGB	Sozialgesetzbuch (Social Code Book)
SMA	spinal muscular atrophy
SMN	survival motor neuron
WHO	World Health Organization

Preliminary note

The Federal Joint Committee (G-BA[2]) is the main decision-maker in the German statutory health insurance system. The Institute for Quality and Efficiency in Health Care (IQWiG[3]), founded in 2004, is the German health technology assessment agency. IQWiG's tasks are specified in Social Code Book (SGB[4]) V, which regulates the statutory health care services. Among other things, IQWiG is commissioned by the G-BA to assess drug and non-drug interventions. IQWiG also assesses new drugs at market entry following the introduction of early benefit assessments in 2011 according to the Act on the Reform of the Market for Medicinal Products (AMNOG[5]). As specified in §35a SGB V[6], "This includes, in particular, the assessment of the added benefit versus the appropriate comparator therapy,[7] the extent of the added benefit and its therapeutic relevance. The benefit assessment is conducted on the basis of evidence provided by the pharmaceutical company, including all clinical trials conducted or commissioned by the company..." IQWiG's tasks were further expanded in 2020 with the Law for More Safety in the Supply of Medicines (GSAV[8]). This law includes several measures to improve drug safety. Among other things it stipulates that, for certain drugs, routine practice data can be used in early benefit assessments. As specified in §35a (3b) SGB V, the G-BA can require the collection of these data from the pharmaceutical company.

Executive summary

On 16 July 2020, the G-BA commissioned IQWiG to develop a concept for a routine practice data collection according to the GSAV (RPDC-GSAV) and for the analysis of these data to inform a decision according to §35a (3b) SGB V on the gene therapy drug onasemnogene abeparvovec.

Research question of the RPDC-GSAV

The following research question arises from the existing need for information for a benefit assessment of onasemnogene abeparvovec, which is to be addressed by the RPDC-GSAV:

- investigation of the long-term added benefit of onasemnogene abeparvovec versus the appropriate comparator therapy for the approved patient population (including patients who are older than 6 months at the time of treatment)

[2] *Gemeinsamer Bundesausschuss* English website: g-ba.de/english/

[3] *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* English website: www.iqwig.de/en/

[4] *Sozialgesetzbuch* German website SGB V: sozialgesetzbuch-sgb.de/sgbv/1.html

[5] *Arzneimittelneuordnungsgesetz* An overview of how the AMNOG procedure is implemented at IQWiG is available in English on iqwig.de/en/presse/media-centre/figures-and-graphs/what-are-dossier-assessments/

[6] German website: sozialgesetzbuch-sgb.de/sgbv/35a.html (quotation translated by IQWiG)

[7] Appropriate comparator therapy = standard care specified by the G-BA

[8] *Gesetz für mehr Sicherheit in der Arzneimittelversorgung* An overview of the law is available in German on the website of the Federal Ministry of Health: bundesgesundheitsministerium.de/gsav.html

The approved patient population is characterized by genetic and clinical features (symptoms). The description of patient groups is currently changing due to changing diagnostics. To specify the appropriate comparator therapy, the G-BA, like the regulatory authority, use both genetic and clinical characteristics and have designated the following patient groups:

- presymptomatic patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene, as well as
  symptomatic patients with 5q SMA type I and II with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
  - appropriate comparator therapy: nusinersen
- symptomatic patients with 5q SMA type III with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
  - appropriate comparator therapy: treatment according to the physician's choice of nusinersen or best supportive care (BSC).

Methods

The development of the concept for an RPDC-GSAV and for the analysis of these data on onasemnogene abeparvovec for the benefit assessment was supported by the following components:

- Search for ongoing and planned data collections (search on regulatory authority websites of the European Medicines Agency [EMA] and the Food and Drug Administration [FDA]).
- Search for disease registries (search in overviews of registries: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [EnCEPP], TREAT-NMD neuromuscular network [list of SMA registries], and Orphanet; focused bibliographic search in MEDLINE for publications on disease registries); request for information on identified registries from registry operators via questionnaire.
- Evaluation of the suitability of the current and planned data collections for answering the research question of the RPDC-GSAV.
- Evaluation of the disease registries on the basis of the criteria of the rapid report A19-43.[9]

Results

Ongoing and planned data collections

In the EMA and FDA documents, ongoing and planned data collections on onasemnogene abeparvovec include 3 interventional 1-arm studies (1 of which has since been completed),

[9] "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)"

3 extension studies for the further follow-up of patients from the interventional studies, and 1 observational study in a patient registry.

Overall, the completed, ongoing and planned interventional studies on onasemnogene abeparvovec cover only part of the population relevant to the RPDC-GSAV. The studies include predominantly symptomatic patients with SMA type I with 2 *SMN2* copies. Data on SMA type II or III are completely missing, as are data on SMA type I with 1 or 3 *SMN2* copies. Data on presymptomatic patients are being investigated in the ongoing study CL-304, but with a small sample size and without inclusion of patients with 1 *SMN2* copy.

In addition, none of the interventional studies involves a comparison, so these studies alone are per se not an appropriate data source for the RPDC-GSAV.

The associated extension studies primarily aim to examine data on long-term adverse effects. In some cases, data on motor and general physical development are also examined. Since the extension studies do not include any other patients relevant to the present research question, they cannot remedy the above-described deficit of the unstudied populations and the lack of comparison with the appropriate comparator therapy.

Overall, the completed and ongoing 1-arm interventional trials, including the associated extension studies, are unsuitable to address the existing evidence gaps. The observational study in a patient registry is considered in the discussion of registries.

Disease registries

The search for disease registries identified 3 registries (RESTORE, SMArtCARE, and the TREAT-NMD global registry with the German SMA patient registry as part of the TREAT-NMD network).

For evaluation of the registries regarding their suitability as a data source for an RPDC-GSAV, additional information from the registry operators was to be used in addition to the publicly available information. For this purpose, the respective contact persons were asked for further information by means of a questionnaire. The operators of the RESTORE registry did not respond to the request for information, while the operators of the SMArtCARE registry and the TREAT-NMD global registry provided information for the assessment.

For the RESTORE registry, several issues remain unclear due to the limited publicly available information as well as the lack of feedback from the registry operators. Irrespective of this, considerable limitations already exist due to the aim of the RESTORE registry, the recruitment of centres, and the type of data collection, so that it can be assumed that the RESTORE registry in its current form is not a suitable data source for an RPDC-GSAV for benefit assessments according to §35a (3b) SGB V.

Overall, the TREAT-NMD global registry, as a meta-registry with a heterogeneous data stock and heterogeneous data quality without a suitable German sub-registry, cannot currently be considered as a primary data source.

On the basis of the available information, the SMArtCARE registry appears to be suitable in principle for an RPDC-GSAV according to §35a SGB V. The data collections are largely conducted in German centres, are comprehensive and are conducted at uniform time points during the observation period. The centres are trained in data collection. However, the SMArtCARE registry also has limitations, which should be considered or eliminated in the context of an RPDC-GSAV (missing collection of data on health-related quality of life, limited inclusion of patients without SMA-specific medication, missing source data verification, possibly required extension [collection of data on confounders]).

Study design and data sources for the RPDC-GSAV

Under the restriction of §35a (3b) SGB V to disease-specific data collections without randomization, non-randomized comparisons within a study (parallel control) or the comparison of single arms of different (single- or multi-arm) studies (parallel or historical control) are eligible.

Studies on nusinersen were identified via a search in ClinicalTrials.gov to judge whether the research question of the RPDC-GSAV, particularly the comparison with nusinersen, could be answered by comparison with single arms from nusinersen studies. The assessment of the available nusinersen studies shows that only the studies of the nusinersen development programme are available for a non-randomized comparison of single arms from different studies. The already available nusinersen study arms cover only part of the relevant patient groups and, moreover, the number of patients included in each case is small. Due to the limited data on nusinersen, the non-randomized comparison of single arms from different studies is not a meaningful approach for the RPDC-GSAV for a benefit assessment of onasemnogene abeparvovec versus nusinersen. Moreover, this study design would hardly be suitable due to methodological considerations. For instance, the comparison of single arms from different studies is generally associated with a risk of bias caused by the use of different data sources (e.g. due to different data collection times or different definitions of data points). In addition, changes in diagnostic and treatment methods must be assumed in the relevant therapeutic indications, for example, due to an earlier start of treatment after newborn screening. Overall, it is also necessary to prospectively collect data on nusinersen for a comparison with onasemnogene abeparvovec.

Since in any case the non-randomized comparison of two drugs has a high risk of bias, the additional potentially biasing factors mentioned above should be avoided. Therefore, under the requirements of §35a (3) SGB V, a non-randomized comparison with a parallel control within one study is recommended for the RPDC-GSAV on onasemnogene abeparvovec.

The SMArtCARE registry currently appears to be the most suitable primary data source for a timely RPDC-GSAV. The RPDC-GSAV can be supported by the inclusion of further (international) registries. The prerequisite for this is that the data collected in the respective registry correspond in scope and quality to the requirements of the RPDC-GSAV and that an analysis can be conducted in accordance with the requirements of the RPDC-GSAV and made available for the benefit assessment. A further prerequisite is that the health care provided in the country in which the data are collected is sufficiently similar to the health care provided in Germany or that the findings obtained from this registry are applicable to the situation in Germany.

Duration and scope of the RPDC-GSAV

The scope of the RPDC-GSAV results from the outcomes to be documented (see PICO [patient/population, intervention, comparison, outcomes] below), the sample size to be followed up (recommendation: approx. 500 patients) and the recommended duration of follow-up (recommendation: 36 months for the assessment of motor development, 60 months for the sustainability of treatment effects).

Data analysis

Rapid report A19-43 describes the general requirements for the analysis of comparative studies without randomization. The planning of the analysis for such studies and thus also for the registry study for the RPDC-GSAV on onasemnogene abeparvovec includes a detailed statistical analysis plan (SAP), which, among others, describes the statistical methods, the handling of missing data, and the conduct of sensitivity analyses.

A key aspect in comparative studies without randomization is the adequate adjustment for confounders. In order to achieve adequate confounder control, it is in particular necessary to identify in advance all important confounders, collect data on them, and consider them in the model. This also applies to the RPDC-GSAV on onasemnogene abeparvovec.

Of the methodological approaches described in rapid report A19-43, the propensity score method appears to be the most suitable for confounder adjustment in the present case. Since different methods can, for example, lead to different degrees of overlap or balance, the decision structure for selecting the specific method can and should be described in the SAP.

Until the approval of onasemnogene abeparvovec, only nusinersen was available among the agents to be considered in the RPDC-GSAV. It is an open question as to whether patients treated with nusinersen prior to the approval of onasemnogene abeparvovec would have been more likely to be treated with onasemnogene abeparvovec if it had been available earlier. It would therefore appear reasonable to plan analyses with and without consideration of data on nusinersen that were collected before the approval of onasemnogene abeparvovec.

SMA is currently a very dynamic therapeutic indication (discussion on the introduction of newborn screening for SMA, new treatment options). Because of the longer survival of

children, motor development may become even more important in the comparative assessment of treatment options. The RPDC-GSAV should react to substantial changes in the evidence available. It is therefore recommended to perform regular, preplanned interim analyses and to discuss their consequence for the ongoing RPDC-GSAV, for example, with regard to sample size and duration of follow-up.

The protocol and SAP for the registry study on the RPDC-GSAV should be the starting point for the inclusion of other registries. The analysis can be performed separately for each registry, and joint analysis is possible as a meta-analysis of the individual registry results. The principles described above apply equally to the analysis within the respective registry.

Conclusion

The concept for an RPDC-GSAV on onasemnogene abeparvovec has the following components:

PICO

Table 1: PICO patient group A for the RPDC-GSAV

P(opulation)	▪ Presymptomatic patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene as well as ▪ Symptomatic patients with 5q SMA type I and II with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.
I(ntervention)	Onasemnogene abeparvovec
C(omparator)	Nusinersen
O(outcome)	Mortality ▪ deaths Morbidity ▪ motor function (recorded with age-appropriate instruments, depending on disease severity, especially achievement of WHO motor development milestones) ▪ respiratory function (need for [permanent] ventilation) ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) ▪ further complications of the disease (e.g. pain, orthopaedic complications) Adverse effects ▪ adverse events Health-related quality of life ▪ health-related quality of life (recorded with an age-appropriate instrument)
RPDC-GSAV: routine practice data collection according to the “Gesetz für mehr Sicherheit in der Arzneimittelversorgung” (Law for More Safety in the Supply of Medicines); SMA: spinal muscular atrophy; SMN: survival motor neuron; WHO: World Health Organization	

Table 2: PICO patient group B for the RPDC-GSAV

P(opulation)	▪ Symptomatic patients with 5q SMA type III with a bi-allelic mutation in the *SMN 1* gene and up to 3 copies of the *SMN2* gene
I(ntervention)	Onasemnogene abeparvovec
C(omparator)	Treatment according to the physician's choice of nusinersen or BSC
O(outcome)	Mortality ▪ deaths Morbidity ▪ motor function (recorded with age-appropriate instruments, depending on disease severity, especially achievement of WHO motor development milestones) ▪ respiratory function (need for [permanent] ventilation) ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) ▪ further complications of the disease (e.g. pain, orthopaedic complications) Adverse effects ▪ adverse events Health-related quality of life ▪ health-related quality of life (recorded with an age-appropriate instrument)
BSC: best supportive care; RPDC-GSAV: routine practice data collection according to the "Gesetz für mehr Sicherheit in der Arzneimittelversorgung" (Law for More Safety in the Supply of Medicines); SMA: spinal muscular atrophy; SMN: survival motor neuron; WHO: World Health Organization	

Type and methods of data collection

- Non-randomized comparison of onasemnogene abeparvovec with the appropriate comparator therapy in a study (parallel control); study protocol and SAP with emulation of the target trial
- Conduct of the studies in a disease registry, currently suitable: SMArtCARE (inclusion of other registries possible under certain conditions)

Duration and scope of data collection

- Duration determined by the necessary follow-up period per patient and the sample size required
  - follow-up of achievable motor development: until Month 36
  - follow-up of the sustainability of the achieved development: until Month 60
  - sample size: exploratory sample size estimate based on the outcome of mortality / permanent ventilation (about 500 patients)
- Scope determined by the outcomes to be recorded and the sample size required

Analysis of data collection

- Examination of the assumptions for the duration and scope of the RPDC-GSAV in the course of data collection; adjustment of planning if necessary
- Analysis with adequate, sufficiently prespecified confounder adjustment (according to Section 5.4.3)

1 Background

Commission to develop a concept for a routine practice data collection according to GSAV for onasemnogene abeparvovec

With the Law for More Safety in the Supply of Medicines (GSAV[10]) in 2019, routine practice data collection according to GSAV (RPDC-GSAV) within the context of the early benefit assessment of drugs according to §35a Social Code Book (SGB[11]) V was introduced [1]. Thus, the Federal Joint Committee (G-BA[12]) can commission an RPDC-GSAV for orphan drugs and for drugs with conditional approval or approval under exceptional circumstances. The aim of such a data collection is to achieve a valid quantification of the added benefit [2]. Comparative investigations are required for this purpose [3]. Accordingly, the G-BA can demand disease-specific data collections without randomization (§35a [3b] Sentence 6 SGB V). Furthermore, if the G-BA requires an RPDC-GSAV from the pharmaceutical company, for orphan drugs too, a dossier must be submitted by the company to prove the added benefit versus the appropriate comparator therapy (§35a [1] Sentence 11 SGB V).

With its decision of 16 July 2020, the G-BA for the first time initiated a procedure for the possible requirement of an RPDC-GSAV, namely for the gene therapy drug onasemnogene abeparvovec in the treatment of spinal muscular atrophy (SMA). In this context, the Institute for Quality and Efficiency in Health Care (IQWiG[13]) was commissioned to develop a scientific concept for an RPDC-GSAV and the analysis of these data to inform a decision according to §35a (3b) SGB V. Onasemnogene abeparvovec was approved as an orphan drug on 1 July 2020 and is currently being evaluated as part of the benefit assessment according to §35a SGB V.

[10] *Gesetz für mehr Sicherheit in der Arzneimittelversorgung*

[11] *Sozialgesetzbuch*

[12] *Gemeinsamer Bundesausschuss*

[13] *Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*

2 Research question of the report

The aim of the present investigation is to develop a concept for an RPDC-GSAV and for the analysis of these data on onasemnogene abeparvovec in the treatment of patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene as well as

- clinically diagnosed SMA type I or
- presence of up to 3 copies of the *SMN2* gene

The concept shall inform a decision according to §35a (3b) SGB V and shall in particular contain requirements for:

- the type, duration and scope of data collection
- the research question (PICO framework: patient/population, intervention, comparison, outcomes) that is to be the subject of the data collection and analyses, including the patient-relevant outcomes to be recorded
- the data collection methods
- the analysis by the pharmaceutical company

For the requirements of the concept, it should be considered that meaningful results can be obtained, among others, on the following aspect relevant to the early benefit assessment:

- data on patient-relevant outcomes that allow assessment of the long-term added benefit and harm of treatment with onasemnogene abeparvovec versus the appropriate comparator therapy for the approved patient population (including patients with 5q SMA who are older than 6 months or 6 weeks at the time of treatment with onasemnogene abeparvovec)

The G-BA specified the following appropriate comparator therapy for this purpose:

- for presymptomatic patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene as well as symptomatic patients with 5q SMA type I and II with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene: nusinersen
- for symptomatic patients with 5q SMA type III with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene: treatment according to the physician’s choice of nusinersen or best supportive care (BSC)

3 Course of the project

On 16 July 2020, the G-BA commissioned IQWiG to develop a concept for an RPDC-GSAV and for the analysis of these data to inform a decision according to §35a (3b) SGB V on onasemnogene abeparvovec. The specification of the appropriate comparator therapy for the RPDC-GSAV on onasemnogene abeparvovec was submitted on 13 August 2020.

The development of the concept was based on a project outline and documented in a rapid report. This report was submitted to the G-BA and published on the IQWiG website together with the G-BA's decision.

4 Methods

The development of the concept for an RPDC-GSAV and for the analysis of these data on onasemnogene abeparvovec for the benefit assessment was supported by the following components:

Information retrieval

Search for ongoing and planned data collections and existing disease registries

- Ongoing and planned data collections
  - search on regulatory authority websites (the European Medicines Agency [EMA] and the Food and Drug Administration [FDA]) for studies on onasemnogene abeparvovec
  - exploratory search for studies on nusinersen in the study registries ClinicalTrials.gov and EU Clinical Trials Register (EU CTR)
- Disease registries
  - search in overviews of registries: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EnCEPP), TREAT-NMD neuromuscular network (list of SMA registries), Orphanet
  - focused bibliographic search in MEDLINE for publications on disease registries
  - request for information on the registries identified from the registry operators via questionnaire
  - inclusion criteria: the registry documents data of patients with SMA; the registry contains at least 1 centre in Germany

Information assessment

Evaluation of the suitability of the current and planned data collections for answering the questions of the RPDC-GSAV

- Comparison of the characteristics of the ongoing and planned data collections with the research question of the RPDC-GSAV; description of the parts of the research question addressed by these data collections and the parts for which no information is expected from these data collections.

Evaluation of the quality of data recording and analysis in the data collections identified

- Evaluation of the disease registries on the basis of the criteria of the rapid report A19-43[14] [3].

[14] "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)"

5 Results

5.1 Need for information for the benefit assessment of onasemnogene abeparvovec

In addition to the information available in the drug approval procedure for onasemnogene abeparvovec, the following need for information arises for the benefit assessment according to §35a SGB V:

- Data on the benefit of onasemnogene abeparvovec versus the appropriate comparator therapy (depending on patient characteristics, nusinersen or treatment according to the physician's choice of nusinersen or BSC) for patient-relevant outcomes describing mortality, morbidity, and health-related quality of life for the approved patient population.
- Data to assess the long-term (added) benefit and harm of treatment with onasemnogene abeparvovec.
- Data to assess the (added) benefit and harm of treatment with onasemnogene abeparvovec in patients with 5q SMA who are older than 6 months at the time of treatment with onasemnogene abeparvovec.

The need for information is justified by the fact that data in comparison with the treatment alternatives nusinersen and BSC are required in health care. Furthermore, for assessment of the benefit and harm of gene therapy with onasemnogene abeparvovec, long-term data are particularly required, as the follow-up period available so far is short and, for example, assessment of the sustainability of treatment success is only possible when the patients have reached further motor milestones or when it can be assessed at which level motor development can be maintained. Since the approved patient population contains no age restriction, but the available studies have so far predominantly included patients younger than 6 months, there is also a need for information on the benefit and harm of treatment in older patients. Adult patients are not considered in the present concept, since it is assumed that adults are treated with onasemnogene abeparvovec only in individual cases [4].

5.2 Research question of the RPDC-GSAV

The following research question arises from the existing need for information for a benefit assessment of onasemnogene abeparvovec, which is to be addressed by the RPDC-GSAV:

- investigation of the long-term added benefit of onasemnogene abeparvovec versus the appropriate comparator therapy for the approved patient population (including patients who are older than 6 months at the time of treatment)

The approved patient population is characterized by genetic and clinical features (symptoms). The description of patient groups is currently changing due to changing diagnostics. To specify the appropriate comparator therapy, the G-BA, as well as the regulatory authority, use both genetic and clinical characteristics and have designated the following patient groups:

- Presymptomatic patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene, as well as
  symptomatic patients with 5q SMA type I and II with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
  - appropriate comparator therapy: nusinersen
- Symptomatic patients with 5q SMA type III with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
  - appropriate comparator therapy: treatment according to the physician's choice of nusinersen or BSC.

This specification of the appropriate comparator therapy results in 2 PICOs, which are described in the following tables.

Table 3: PICO patient group A for the RPDC-GSAV

P(opulation)	▪ Presymptomatic patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene as well as ▪ Symptomatic patients with 5q SMA type I and II with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.
I(ntervention)	Onasemnogene abeparvovec
C(omparator)	Nusinersen
O(outcome)	Mortality ▪ deaths Morbidity ▪ motor function (recorded with age-appropriate instruments, depending on disease severity, especially achievement of WHO motor development milestones) ▪ respiratory function (need for [permanent] ventilation) ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) ▪ further complications of the disease (e.g. pain, orthopaedic complications) Adverse effects ▪ adverse events Health-related quality of life ▪ health-related quality of life (recorded with an age-appropriate instrument)
RPDC-GSAV: routine practice data collection according to the "Gesetz für mehr Sicherheit in der Arzneimittelversorgung" (Law for More Safety in the Supply of Medicines); SMA: spinal muscular atrophy; SMN: survival motor neuron; WHO: World Health Organization	

Table 4: PICO patient group B for the RPDC-GSAV

P(opulation)	▪ Symptomatic patients with 5q SMA type III with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
I(ntervention)	Onasemnogene abeparvovec
C(omparator)	Treatment according to the physician's choice of nusinersen or BSC
O(outcome)	Mortality ▪ deaths Morbidity ▪ motor function (recorded with age-appropriate instruments, depending on disease severity, especially achievement of WHO motor development milestones) ▪ respiratory function (need for [permanent] ventilation) ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) ▪ further complications of the disease (e.g. pain, orthopaedic complications) Adverse effects ▪ adverse events Health-related quality of life ▪ health-related quality of life (recorded with an age-appropriate instrument)
BSC: best supportive care; RPDC-GSAV: routine practice data collection according to the "Gesetz für mehr Sicherheit in der Arzneimittelversorgung" (Law for More Safety in the Supply of Medicines); SMA: spinal muscular atrophy; SMN: survival motor neuron; WHO: World Health Organization	

The study duration required depends on the number of observed events needed to describe effects of the interventions with the necessary certainty for quantifying the added benefit. Furthermore, in the present therapeutic indication it is relevant up to what age the patients should be followed up, so that benefit and harm can be adequately described (see Section 5.4.2).

5.3 Data sources available

Whether it makes sense to conduct an RPDC-GSAV depends on, among other things, which of the existing information gaps for quantifying the added benefit can potentially be closed by data collections already ongoing or planned. When planning an RPDC-GSAV, it is also relevant whether this data collection can be conducted by modifying or expanding an ongoing or planned data collection. In this context, according to §35a SGB V, data collections resulting from requirements of regulatory and other approval authorities are of particular importance. In addition, it is relevant whether suitable disease registries are already available for the data collection, because this can considerably shorten the time until the RPDC-GSAV begins.

Therefore, in the following text, the current and planned data collections from the requirements of regulatory and other approval authorities are first described and analysed (Section 5.3.1). Subsequently, disease registries are described and their suitability for the RPDC-GSAV evaluated (Section 5.3.2).

5.3.1 Ongoing and planned data collections on onasemnogene abeparvovec from requirements of regulatory and other approval authorities

Search for ongoing and planned data collections on onasemnogene abeparvovec

Ongoing and planned data collections from requirements of regulatory and other approval authorities were searched for on the websites of the EMA and the FDA (search on 24 July 2020). For the EMA, the European Public Assessment Report (EPAR [5]) and the summary of the Risk Management Plan (RMP [6]) of onasemnogene abeparvovec were considered. The FDA requirements were extracted from the Summary Basis for Regulatory Action [7] and the Pharmacovigilance Plan Review Memorandum [8] of onasemnogene abeparvovec.

The EMA documents describe the following data collections:

- Designated as a prerequisite for approval
  - completion of the AVXS-101-CL-302, AVXS-101-CL-303 and AVXS-101-CL-304 studies already assessed for approval, designated by the EMA as post-authorization efficacy studies (PAES)
  - conduct of a prospective non-interventional observational study in a patient registry (AVXS-101-RG-001), designated by the EMA as a non-interventional post-authorization efficacy study (PAES)
- Designated as further studies in the development programme after approval
  - the AVXS-101-LT-001 study on the further follow-up of patients included in the AVXS-101-CL-101 study
  - the AVXS-101-LT-002 study on the further follow-up of patients with SMA type I who were treated with onasemnogene abeparvovec in studies

Of the studies mentioned, study CL-303 has since been completed [9].

The FDA documents describe the data collections listed below. The FDA points out that these data collections are studies that the pharmaceutical company is conducting voluntarily and are not FDA requirements.

- 3 long-term follow-up studies of patients who were treated with onasemnogene abeparvovec in interventional studies (“non-interventional, observational studies collecting long-term follow-up safety data”)
  - the AVXS-101-LT-001 study on the further follow-up of patients included in the AVXS-101-CL-101 study
  - the AVXS-101-LT-002 study on the further follow-up of patients with SMA type I, II or III who were treated with onasemnogene abeparvovec in studies (in deviation from the study description of the EMA, SMA type II or III are also included here)

  - the AVXS-101-LT-003 study on the further follow-up of patients with SMA with 3 or 4 copies of the *SMN2* gene who were treated with onasemnogene abeparvovec in studies
- a prospective, non-interventional observational study in a patient registry (AVXS-101-RG-001)

In summary, 3 interventional 1-arm studies (1 of which has now been completed), 3 extension studies for the further follow-up of patients from the interventional studies, and 1 observational study in a patient registry are designated as ongoing and planned data collections in the EMA and FDA documents.

Characterization of data collections on onasemnogene abeparvovec

The following Table 5 describes the most important study characteristics of the data collections designated by the EMA and the FDA. Information that did not emerge from the EMA [5,6] or FDA [7,8] documents was supplemented by information from the study registry entry for the respective study in the ClinicalTrials.gov study registry (http://www.clinicaltrials.gov) [9-14].

Table 5: Characteristics of the data collections designated by EMA and FDA(multi-page table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study conduct	Outcomes[a]
Interventional 1-arm studies (ongoing)						
AVXS-101-CL-302 (STRIVE-EU)	Phase III, open, 1-arm	Children < 6 months (< 180 days)[b] with SMA type I with a bi-allelic mutation in the *SMN1* gene and with 1 or 2 copies of the *SMN2* gene[c]	Onasemnogene abeparvovec (data cut-off 31.12.2019: N = 33) thereof: 1 *SMN2* copy: n = 0 2 *SMN2* copies: n = 33	Screening: 28 days Treatment: one-time infusion with onasemnogene abeparvovec i.v. Follow-up: up to the age of 18 months	EU, so far 9 centres in Belgium, France, Italy, United Kingdom Q2 2018–ongoing	Primary: ▪ Number of participants who achieve independent sitting for at least 10 seconds at 18 months of age[d] Secondary: ▪ Event-free survival[e] at 14 months of age Exploratory: ▪ Achievement of motor development milestones ▪ CHOP-INTENT ▪ Bayley Scales of Infant and Toddler Development ▪ Adverse effects

Table 5: Characteristics of the data collections designated by EMA and FDA(multi-page table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study conduct	Outcomes[a]
AVXS-101-CL-304 (SPRINT)	Phase III, open, 1-arm	Presymptomatic patients with a bi-allelic *SMN1* deletion and with 2, 3 or 4 copies[f] of the *SMN2* gene[g]	Onasemnogene abeparvovec (data cut-off 31.12.2019: N = 29) Thereof: Cohort 1 (2 *SMN2* copies) (n = 14) Cohort 2 (3 *SMN2* copies) (n = 15)	Screening: 28 days Treatment: one-time infusion with onasemnogene abeparvovec i.v. Follow-up: ▪ Cohort 1: up to an age of 18 months ▪ Cohort 2: up to an age of 24 months	Multicentre, 29 studies globally, thereof 14 in the USA, 1 in Germany Ongoing	▪ Survival[h] ▪ Motor development milestones ▪ Bayley Scales of Infant and Toddler Development ▪ CHOP-INTENT ▪ Cohort-specific: ▫ Cohort 1 (2 *SMN2* copies): percentage of participants achieving functional independent sitting for at least 30 seconds at any visit at 18 months of age ▫ Cohort 2 (3 *SMN2* copies): percentage of participants achieving the ability to stand without support for at least 3 seconds at any visit at 24 months of age ▪ Adverse effects

Table 5: Characteristics of the data collections designated by EMA and FDA(multi-page table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study conduct	Outcomes[a]
Interventional 1-arm studies (completed)						
AVXS-101-CL-303 (STRIVE-US)	Phase III, open, 1-arm	Children < 6 months (< 180 days)[b] with symptomatic or presymptomatic SMA type I without functional *SMN1* gene[i] and with 1 or 2 copies of the *SMN2* gene[c]	Onasemnogene abeparvovec (N = 22) Thereof: 1 *SMN2* copy: n = 0 2 *SMN2* copies: n = 22	Screening: up to 30 days Treatment: 31 days (one-time infusion with onasemnogene abeparvovec i.v.; concomitant treatment with prednisolone: the day before infusion until 30 days after infusion) Follow-up: up to the age of 18 months	16 centres in the USA 2017–12/2019	Primary: ▪ Percentage of participants with achievement of independent sitting for at least 30 seconds at 18 months of age[j] ▪ Event-free survival[e] at 14 months of age Secondary: ▪ Percentage of participants with ability to thrive[k] at 18 months of age. ▪ Percentage of participants with ventilatory support independence at 18 months of age Exploratory: ▪ Percentage of participants achieving motor development milestones[l] ▪ Bayley Scale of Infant and Toddler Development (Version 3), subscales for fine and gross motor skills ▪ CHOP-INTEND ▪ Adverse effects

Table 5: Characteristics of the data collections designated by EMA and FDA(multi-page table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study conduct	Outcomes[a]
Extension studies						
AVXS-101-LT-001	Observational study, safety follow-up	Patients with SMA type I who received gene replacement therapy with onasemnogene abeparvovec in the CL-101 study	N = 13 No further gene replacement therapy, nusinersen can be administered	Initial observation phase (annual visit): 5 years subsequent follow-up (annual telephone contact): 10 years	USA, Nationwide Children's Hospital, Columbus Long-term follow-up, ongoing	Primary: ▪ Collection of long-term safety data (SAEs and AEs of special interest) Secondary: ▪ Percentage of participants able to maintain their highest motor development milestone achieved in study CL-101[m]
AVXS-101-LT-002[n]	Observational study	Patients with SMA type I who received onasemnogene abeparvovec in clinical trials	Planned: N ≤ 85	Initial observation phase (annual visit): 5 years subsequent follow-up (annual telephone contact): 10 years	Long-term follow-up Q4 2018–ongoing	▪ Gene therapy-related late AEs (SAEs, AEs of special interest) ▪ Number of participants who reach developmental milestones[o] ▪ Change from baseline in HFMSE score ▪ Other outcomes used to assess physical development[p]
AVXS-101-LT-003	Observational study	Patients with SMA with 3 or 4 copies of the *SMN2* gene who received onasemnogene abeparvovec in a clinical trial	Planned: N ≤ 85	Initial follow-up phase (annual visit): 5 years Subsequent follow-up (annual telephone contact): 10 years	Long-term follow-up Q2 2018–ongoing	▪ Gene therapy-related late AEs, SAEs, AEs of special interest

Table 5: Characteristics of the data collections designated by EMA and FDA(multi-page table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study conduct	Outcomes[a]
Prospective, non-interventional observational study in a patient registry						
AVXS-101-RG-001 (RESTORE)	Prospective observational study in a patient registry	Patients with SMA (all types)	Inclusion of all patients treated with onasemnogene abeparvovec over a 5-year recruitment period; other interventions not reported. Planned: N ≥ 500	15 years	Multicentre, 26 recruiting centres in the USA Long-term follow-up 06/2018–ongoing	▪ Overall survival ▪ SAEs, AEs of special interest ▪ Motor development milestones and function ▪ Ventilatory support-free survival

Table 5: Characteristics of the data collections designated by EMA and FDA(multi-page table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study conduct	Outcomes[a]

a. Partly without information on the classification into primary and secondary (clinically relevant) outcomes.
b. At the time of the one-time infusion with onasemnogene abeparvovec (Day 1).
c. Including the known *SMN2* gene modifier mutation c.859G>C.
d. According to WHO motor development milestones.
e. Defined as averting the combined outcome consisting of either death or permanent ventilation (tracheostomy or need for noninvasive respiratory support ≥ 16 hours/day for ≥ 14 consecutive days in the absence of acute reversible illness; perioperative ventilation excluded). Permanent ventilation is considered a surrogate for the outcome of death.
f. With the modification of the study protocol in September 2018, presymptomatic patients with 4 copies of the *SMN2* gene were no longer included in the study. Up to this point, no patient with 4 gene copies was included. However, the presence of 4 *SMN2* gene copies was subsequently identified for one patient already included in the study.
g. Discrepant information is available on the inclusion of patients with the *SMN2* gene modifier mutation c.859G>C or gene modifying *SMN1* point mutations. None of these patients were included in the efficacy analysis set.
h. Combined outcome of death and need for permanent ventilation.
i. Bi-allelic deletion or point mutation in the *SMN1* gene.
j. According to the Bayley Scale of Infant and Toddler Development (Version 3): sitting upright with head elevated for at least 30 seconds.
k. Ability to swallow thin liquids independently (swallow test) and maintain weight (> 3rd percentile according to WHO Child Growth Standards for age and gender) without relying on gastrostomy or other mechanical or non-mechanical feeding support.
l. Keep head upright without support, roll from back to both sides, sit independently with support (> 10 seconds; WHO), ability to crawl, pull to standing up, stand with support as well as stand alone, walk with support, walk alone.
m. According to the Bayley Scales of Infant and Toddler Development and WHO-MGRS. Documented at baseline and at annual visits during the initial follow-up period.
n. Discrepancies in population, number of patients, and start date between EMA and FDA data on the one hand and in the ClinicalTrials.gov study registry (NCT04042025) on the other. The data from the regulatory documents are shown.
o. Head control, sitting with support, sitting without support, sitting with support for 30 seconds, crawling on hands and knees, pull to standing up, stand with support, walk with support, stand alone, walk alone.
p. Number of participants who experience a clinically significant change from baseline in pulmonary assessment results, physical examination findings, vital signs measurements, clinical laboratory assessments, cardiac assessments, height and weight measurements, and observational phase questionnaire results (questionnaire includes 7 yes/no questions; observation categories include: AEs, hospitalizations, concomitant medications, ventilatory support, and feeding support) as well as number of patients who experience swallowing dysfunction.

AE: adverse event; CHOP-INTENT: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EMA: European Medicines Agency; EPAR: European Public Assessment Report; FDA: Food and Drug Administration; HFMSE: Hammersmith Functional Motor Scale – Expanded; i.v.: intravenous; MGRS: Multicentre Growth Reference Study; n: subpopulation; N: number of patients included; PAES: post-authorization efficacy study; PNCR: Paediatric Neuromuscular Clinical Research; Q: quarter; SAE: serious adverse event; SMA: spinal muscular atrophy; SMN: survival motor neuron; WHO: World Health Organization

The patient registry used to conduct the AVXS-101-RG-001 observational study is the RESTORE registry [15]. This registry is described in Section 5.3.2.

Table 6 below shows the SMA populations (symptoms, SMA type, number of *SMN2* copies) covered by the interventional studies. In the overview, the completed approval study AVXS-101-CL-101 was added, which is listed as a completed study in the EMA EPAR [5]. The associated extension studies are not listed separately, as they do not include additional patients relevant to the present research question.

Table 6: Assignment of data collections to onasemnogene abeparvovec (interventional 1-arm studies).

	Presymptomatic (≤ 3 *SMN2* copies)			**Symptomatic, SMA type I (≤ 3 *SMN2* copies)**			**Symptomatic, SMA type II (2-3 *SMN2* copies)**		**Symptomatic, SMA type III (2-3 *SMN2* copies)**	
	1 copy	**2 copies**	**3 copies**	**1 copy**	**2 copies**	**3 copies**	**2 copies**	**3 copies**	**2 copies**	**3 copies**
Study		CL-304 Cohort 1 (n = 14)	CL-304 Cohort 2 (n = 15)		CL-101 Cohort 2 (n = 12)[a] CL-302 (n = 33) CL-303 (n = 22)					
In each case, the abbreviated form of the study name is indicated (e.g.: CL-101 instead of AVXS-101-CL-101). a. A total of 15 patients were included in the CL-101 study. Three of the 15 patients in Cohort 1 were treated with an off-label dose.										

From the overview, it is clear that the conducted, ongoing and planned interventional studies of onasemnogene abeparvovec cover only part of the population relevant to the RPDC-GSAV. The studies include predominantly symptomatic patients with SMA type I and 2 *SMN2* copies. Data on SMA type II or III are completely missing, as are data on SMA type I with 1 or 3 *SMN2* copies. Data on presymptomatic patients are being investigated in the ongoing CL-304 study, but with a small sample size and without inclusion of patients with 1 *SMN2* copy. In general, the number of patients included is small.

In addition, none of the interventional studies involves a comparison, so these studies alone are per se not an appropriate data source for the RPDC-GSAV.

The associated extension studies primarily aim to examine data on long-term adverse effects. In some cases, data on motor and general physical development are also examined. Since the extension studies do not include any other patients relevant to the present research question, they cannot remedy the above-described deficit of the unstudied populations and the lack of comparison with the appropriate comparator therapy.

Overall, the completed and ongoing 1-arm interventional trials, including the associated extension studies, are unsuitable to address the existing evidence gaps

5.3.2 Registries as a potential data source for the RPDC-GSAV

The analysis presented in IQWiG's rapid report A19-43[15] showed that, besides study-specific data collection,[16] registries in particular can represent a suitable data source for an RPDC-GSAV [3]. The prerequisite for this is that the respective registry can provide the necessary data in sufficient quality. In addition to data collection, this includes, among other things, the planning, analysis and publication of the results of the associated registry study. A registry study in a suitable registry represents a structured implementation of the RPDC-GSAV.

In the following text, the result of the search for potentially suitable registries for the RPDC-GSAV is first described (Section 5.3.2.1). The registries identified in this way are described in Section 5.3.2.2. The evaluation of the identified registries with regard to their suitability for an RPDC-GSAV on onasemnogene abeparvovec for a benefit assessment according to §35a (3b) SGB V is described in Section 5.3.2.3.

5.3.2.1 Result of the search for disease registries

The search for disease registries on SMA was conducted on the websites of EnCEPP (http://www.encepp.eu), TREAT-NMD (http://www.treat-nmd.org) and Orphanet

[15] "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)"

[16] That is, the specific conduct of studies to generate routine practice data for the benefit assessment of drugs.

(https://www.orpha.net/) (search in calendar week 32/2020). In addition, a focused search was conducted in MEDLINE (search on 29 July 2020, see Appendix A for the search strategy).

The search of the EnCEPP website yielded a total of 144 hits. Through this search, the SMArtCARE registry was identified as a potentially relevant data source (http://www.smartcare.de).

The search on the TREAT-NMD website yielded 51 hits. Through this search, the TREAT-NMD SMA global registry (http://www.treat-nmd.org or https://www.treat-nmd.de/register/index.de.html), which includes the German SMA patient registry at the Friedrich Baur Institute, University Hospital Munich, was identified as a potentially relevant data source.

The search on the Orphanet website yielded 69 hits. This search also identified the TREAT-NMD network with the German SMA patient registry.

The focused search yielded 90 hits. Through this search, on the one hand, publications on the already known registries SMArtCARE (Pechmann 2019 [16]) and the TREAT-NMD SMA global registry (Bladen 2014 [17], König 2019 [18], Verhaart 2017 [19]) were identified. On the other, the RESTORE registry with its associated publication Finkel 2020 [15] was additionally identified.

In summary, 3 disease registries were identified by the search. The result of the search for disease registries is summarized in Table 7.

Table 7: Results of the search for disease registries

Data source	**Disease registries identified that include German centres**	**Reference**
EnCEPP	▪ SMArtCARE registry	▪ http://www.smartcare.de
TREAT-NMD	▪ TREAT-NMD SMA global registry with the German SMA patient registry as part of the TREAT-NMD network	▪ http://www.treat-nmd.org; https://www.treat-nmd.de/register/index.de.html
Orphanet	▪ TREAT-NMD SMA global registry with the German SMA patient registry as part of the TREAT-NMD network	▪ http://www.treat-nmd.org; https://www.treat-nmd.de/register/index.de.html
Focused search in MEDLINE	▪ RESTORE registry ▪ SMArtCARE registry ▪ TREAT-NMD SMA global registry with the German SMA patient registry as part of the TREAT-NMD network	▪ Finkel 2020 [15] ▪ Pechmann 2019 [16] ▪ Bladen 2014 [17], König 2019 [18], Verhaart 2017 [19]

5.3.2.2 Registry characteristics

RESTORE registry

The RESTORE registry is a prospective disease registry for SMA. The registry is sponsored by the pharmaceutical company producing onasemnogene abeparvovec, is listed under study number AVXS-101-RG-001, and is part of the requirements in the EMA's Risk Management Plan for onasemnogene abeparvovec [6]. The RESTORE registry is primarily focused on the inclusion of patients treated with onasemnogene abeparvovec: the stated goal is that all patients treated with onasemnogene abeparvovec should be included in the registry. Patients treated with other treatment options may also be included [15].

Patients are to be recruited over a 5-year period and followed up for up to 15 years. A minimum of 500 patients are to be recruited. Recruitment started in September 2018.

SMArtCARE registry

The SMArtCARE registry emerged from a joint initiative of neurologists, neuropaediatricians and patient organizations in the German-speaking regions. The aim of the SMArtCARE registry is to collect observational data on patients with SMA in a standardized way [16]. The SMArtCARE registry was founded in the course of the approval of nusinersen. It is intended to include not only patients with nusinersen, but patients with SMA in general. The registry was initially supported by the Biogen company, an extension of the sponsorship to other pharmaceutical companies is planned.

Patient recruitment started in July 2018. At least 1000 patients are to be recruited.

TREAT-NMD SMA global registry

TREAT-NMD (Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disease) is a global network of partner organizations in the field of neuromuscular diseases. The TREAT-NMD network was established in 2007 and was originally funded by the EU. The TREAT-NMD network's scope of work includes several projects, including the establishment of harmonized international patient registries for various neuromuscular diseases.

The TREAT-NMD SMA global registry is a meta-registry that combines anonymized data from various national SMA registries. The respective national registries are responsible for data collection. The German SMA patient registry at the Friedrich Baur Institute, Munich, is one of these national registries.

For the purpose of harmonization, a core data set for SMA was defined [20]. This data set was expanded in 2018 (V1) and implemented in 12 pilot registries, and another amendment to the data set is currently being processed (V2). The project to extend the core data set is funded by Biogen, the marketing authorization holder of nusinersen [20].

5.3.2.3 Evaluation of the suitability of the registries identified as a data source for an RPDC-GSAV for benefit assessments according to §35a SGB V

5.3.2.3.1 Information sources to evaluate the suitability of registries

For evaluation of the registries regarding their suitability as a data source for an RPDC-GSAV, additional information from the registry operators was to be used in addition to the publicly available information mentioned in Table 7. For this purpose, the respective contact persons were asked for further information by means of a questionnaire.

The questionnaire consisted of 4 sections, of which the first 3 were uniform for all 3 queried registries, RESTORE, SMArtCARE, and the TREAT-NMD SMA global registry. The fourth section of the questionnaire asked registry-specific questions. The query to SMArtCARE was in German and the query to TREAT-NMD and RESTORE was in English.

The following text shows what further information was provided by the individual registry operators. The corresponding completed questionnaires can be found in Appendix B.

Response from the RESTORE registry

Despite a request, no response was provided by the RESTORE registry.

Response from the SMArtCARE registry

For the SMArtCARE registry, the registry operators submitted the following documents in addition to the completed questionnaire:

- registry protocol
- data dictionary
- paper case report forms (CRFs), not filled in
- publication on the SMArtCARE registry (Pechmann 2019 [16])

Response from the TREAT-NMD SMA global registry

The registry operators of the TREAT-NMD SMA global registry submitted the completed questionnaire and referred to the representatives of the German SMA patient registry for the questions concerning Germany or the German SMA registry. These had already been contacted initially and in parallel to the international representatives of the TREAT-NMD SMA global registry and had been asked for the corresponding information.

In an e-mail dated 6 September 2020, the German SMA patient registry informed IQWiG, among other things, that the registry did not include a longitudinal outcome measurement, and therefore referred to the SMArtCARE registry as a potentially relevant data source. Further information on the questions concerning Germany or the German SMA patient registry was not provided, despite a request.

5.3.2.3.2 Suitability evaluation, taking into account nationally and internationally used quality criteria for registries

According to IQWiG's rapid report A19-43, nationally and internationally largely consistent quality criteria can be derived for registries [3]. Appendix C presents an evaluation of the fulfilment of these quality criteria for the two registries RESTORE and SMArtCARE. For the meta-registry TREAT-NMD SMA global registry, a presentation of the quality criteria was omitted because, according to the feedback provided by the registry operators of the meta-registry in Appendix B.3, this depends on the individual quality of each national registry and therefore a heterogeneous quality of the national registries can be assumed. A presentation of the quality criteria related to the meta-registry is therefore not meaningful.

The overall evaluation of the fulfilment of the quality criteria based on the information available shows that all 3 registries have limitations. However, with regard to the question as to whether the respective registry can represent the primary data source for an RPDC-GSAV according to §35a SGB V, there are different degrees of limitations.

For the RESTORE registry and the TREAT-NMD SMA global registry, the limitations are considerable. On the one hand, it can therefore be assumed that the data collected so far in these registries are largely unsuitable for an RPDC-GSAV (retrospective analysis). On the other, fundamental changes to the registry structure would be required in each case in order to establish registry suitability for a prospective RPDC-GSAV and the analysis of these data according to §35a SGB V.

In contrast, the limitations of the SMArtCARE registry are much less pronounced. On the one hand, they probably do not preclude the basic usability of the registry data already collected, although these do not cover the entire spectrum of the research questions of the RPDC-GSAV. On the other, the adjustments to be recommended do not affect the basic registry structure.

In the following text, the evaluation of the RESTORE and the TREAT-NMD SMA global registry is presented. The limitations of the SMArtCARE registry are presented afterwards.

RESTORE registry

For the RESTORE registry, some issues remain unclear due to the limited publicly available information as well as the lack of feedback from registry operators. Irrespective of this, considerable limitations already exist due to the aim of the RESTORE registry, the recruitment of centres, and the type of data collection, so that it can be assumed that the RESTORE registry in its current form is not a suitable data source for an RPDC-GSAV for benefit assessments according to §35a (3b) SGB V.

Aim of the RESTORE registry

The registry is sponsored by the pharmaceutical company producing onasemnogene abeparvovec and is part of the requirements in the EMA's Risk Management Plan for onasemnogene abeparvovec [6]. For onasemnogene abeparvovec only, the reported recruitment

goal is to include all patients treated with this agent, although in principle patients with any treatment can be included in the registry [15]. Differences are therefore likely in the completeness of included patients between onasemnogene abeparvovec on the one hand and nusinersen on the other, combined with a selection bias that can hardly be resolved. Finkel 2020 states that all patients diagnosed with SMA should be consecutively included in the registry so as to reduce selection bias. However, how this is to be achieved, given the nature of the inclusion of international registries in conjunction with the omission of any specifications (see below under "Centre recruitment"), remains unclear. Finkel 2020 and the study registry entry for RESTORE provide no information on this aspect nor on the current recruitment rate for the various treatment options.

In addition, according to Finkel 2020, the collection of data on adverse events of special interest primarily includes those identified as (potential) safety risks of onasemnogene abeparvovec, namely thrombocytopenia, hepatotoxicity, and cardiac events.

Centre recruitment

On the one hand, data collection is to take place in *de novo* centres, while on the other, it is planned to obtain data or analyses from already existing registries, including the SMArtCARE registry and the TREAT-NMD SMA global registry. However, as shown by the feedback on these two registries, transmission of analyses has not yet been agreed upon for either registry more than 2 years after the establishment of the RESTORE registry, and transmission of individual patient data (IPD) will apparently in principle not be possible for either registry (see Appendix B).

According to the entry in ClinicalTrials.gov, no *de novo* centres in Germany have been recruited so far, but almost exclusively centres in the USA [10]. According to an international analysis, there are relevant differences in the care of SMA patients between different countries [17]. This also applies to the comparison of countries with a more developed health care system. Therefore, it remains open at present whether conclusions on the German health care context can be derived at all from the RESTORE registry.

Data collection

The list of registry variables used in RESTORE and reported in Finkel 2020 is extensive. With the exception of the deficits described above regarding the collection of data on adverse events of special interest, it appears sufficient for a registry study in the field of SMA, subject to a detailed examination using a registry protocol. However, the registry variables mentioned are apparently only binding for the *de novo* centres. When data or centres from other registries are included in the RESTORE registry (either as analyses within the registries or by providing IPD), the RESTORE registry apparently does not intend to standardize the scope of the data collection overall, but rather to use the data stock of the respective registries. It is not apparent whether, and if so, what measures are taken to ensure the completeness and accuracy of the data received from other registries.

For the *de novo* centres too, it is largely not ensured that the data collected will be suitable for a comparative analysis of onasemnogene abeparvovec with nusinersen, irrespective of the problem of patient selection described under "Aim of the RESTORE registry". This is because it is not apparent that results on relevant outcomes for the different patients on the one hand and for the different treatment options on the other are collected with similar frequency and at comparable time points. On the contrary, it can be deduced from Finkel 2020 that the centres collect data solely according to their respective local practice and that there is no standard for visits, tests or examinations. Finally, Finkel 2020 notes that the RESTORE registry is limited by the lack of standardized training for the neuromuscular therapists involved and the general lack of standardization of medical examinations.

Overall, the data collection in the RESTORE registry in its current form is not compatible with the conduct of a registry study for an RPDC-GSAV according to §35a SGB V (comparative registry study between onasemnogene abeparvovec and the appropriate comparator therapy).

TREAT-NMD SMA global registry with the German SMA patient registry

Current status

For the TREAT-NMD SMA global registry, the question of suitability for an RPDC-GSAV cannot be answered in a general way. The national registries linked in this meta-registry are each responsible for their own data collection. Accordingly, there is no common registry protocol, but reference is made to the different registry protocols of the participating registries (see Appendix B.3). Training, audits, plausibility checks of the data etc. are also currently the responsibility of the national registries. According to the information it provided, the German SMA patient registry at the Friedrich Baur Institute, Munich, does not collect longitudinal data and is therefore, in principle, unsuitable as a platform for RPDC-GSAV in its current form.

According to the operators of the TREAT-NMD SMA global registry, the type and scope of data collection, as well as the general data quality, are foreseeably heterogeneous. However, due to the lack of access to IPD, this cannot at present be examined in detail by the operators of the meta-registry and thus cannot be addressed on a registry-specific basis. Temporary extensions of the data set for specific registry studies are in principle possible, but their inclusion is also the responsibility of the national registries.

As a meta-registry with a heterogeneous data pool and heterogeneous data quality without a suitable German sub-registry, the TREAT-NMD SMA global registry cannot be considered a primary data source at present.

Future planning

In order to harmonize and prepare for future comparative registry studies, the existing core data set of the SMA registries in the TREAT NMD network will be expanded in iteration stages. In addition, a common optional registry platform will be established (see Appendix B.3). The first version (V1) of the extended core data set from 2018 was tested in 12 pilot centres. The second version (V2) is to be adopted by the end of 2020. It is planned to implement the common

optional registry platform, which will also include standardized plausibility checks, in the summer of 2021.

The extent to which individual country-specific registries of the TREAT-NMD network (especially those that have as pilot centres already implemented V1 of the core data set and will implement V2 in the near future) can supplement the RPDC-GSAV currently remains open and can also currently be left open for the planning of the RPDC-GSAV. For the individual national registries, their suitability (assuming sufficient similarity of the respective health care provided to that provided in Germany) would have to be examined in each case. The prerequisites for the inclusion of individual registries, including those considered in the TREAT-NMD network, are described in Section 5.4.1.2.

SMArtCARE registry

On the basis of the available information, the SMArtCARE registry appears to be suitable in principle for an RPDC-GSAV according to §35a SGB V. The data collections are largely conducted in German centres, are comprehensive and are conducted at uniform time points for the observational data. The centres are trained in data collection.

Approximately 750 patients were included in the registry by the end of August 2020 (see Appendix B.2). According to information provided by telephone by the registry operators, the target value of 1000 patients stated in the registry protocol does not represent an upper limit, but can be extended depending on the requirements for the registry and thus within the framework of an RPDC-GSAV.

However, the SMArtCARE registry also has limitations that should be taken into account or eliminated within the framework of an RPDC-GSAV:

Collection of data on health-related quality of life

So far, health-related quality of life has not been a component of data collection in the SMArtCARE registry. However, a corresponding expansion is possible in principle and, according to the registry operators, is to be supported by technical expansion (direct entry by patients or their relatives, see also Appendix B.2). However, any subsequent addition will remain without consequence for the already existing data sets, as it cannot be assumed that data on health-related quality of life have been systematically collected in the participating centres since 2018. Retrospective analyses of the outcome “health-related quality of life” are therefore not currently possible on the basis of the SMArtCARE registry.

Inclusion of patients without SMA-specific drug therapy

For patients with SMA type III, besides nusinersen, BSC can also be considered as an appropriate comparator therapy within the framework of treatment according to the physician’s choice. Although the SMArtCARE registry is in principle open for the inclusion of all SMA patients, it is noticeable that according to the information provided in the questionnaire by the registry operators, patients treated with BSC are not included in the SMArtCARE registry (see

Appendix B.2). In a telephone call to clarify this discrepancy, the registry operators stated that "about 20 to 30" such patients are included in the SMArtCARE registry. However, willingness to participate in the SMArtCARE registry is low among those not treated with nusinersen or onasemnogene abeparvovec. The SMArtCARE registry is therefore currently hardly suitable for a retrospective comparison of onasemnogene abeparvovec with BSC. Prospective data collection would require recruitment efforts to promote the inclusion of such patients.

Source data verification

With regard to data quality, the SMArtCARE registry currently uses, in particular, standardization of data collection, training of the persons responsible in the centres, plausibility checks during data entry and queries in case of abnormalities. This is a sensible combination and increases the probability of high data quality [3].

Audits to determine and describe the quality of the IPD (accuracy and completeness) by comparison with the source data (source data verification) have not been conducted so far, as, according to the registry operator, no budget is available for this purpose (see Annex B.2).

For the RPDC-GSAV, a source data verification would be meaningful based on a sample of, for example, 5% or 10% of the data sets [3]. This check can be limited to the data fields relevant to the RPDC-GSAV. Such a check should ideally be performed before the start of the prospective data collection, for example, in parallel to the development of the protocol and SAP for the registry study, as any systematic errors can then be identified and corrected in advance. If this is not possible, a check in parallel with the data collection would be meaningful, as it allows the quality of the subsequent data to be estimated.

Potential confounders

The SMArtCARE registry records various items of information that can potentially be used to adjust for confounders. These include comorbidities, number of *SMN2* copies, age at symptom onset (for symptomatic patients) and disease duration. Which confounders are relevant for the research questions in the context of the RPDC-GSAV would have to be clarified in advance during the development of the protocol and the SAP of the registry study by means of a literature research and the involvement of experts [3]. If the potential confounders identified in this way are not completely contained in the data set, retrospective analyses with the existing data sets might not be meaningful, depending on the importance of the missing potential confounders. For the prospective data collection, relevant confounders identified additionally should be added.

At this point, we refer to the current collection of data on comorbidities by means of ICD-10 coding. It seems meaningful to check, in terms of content and also by means of source data verification, whether this coding is sufficiently detailed for the description of comorbidities in the present therapeutic indication of SMA, or whether the goal of a complete and correct representation of the relevant potential confounders could be better ensured by a specific collection of data on single, particularly relevant comorbidities.

5.4 RPDC-GSAV according to §35a (3b) SGB V

5.4.1 Type of RPDC-GSAV

5.4.1.1 Study design of RPDC-GSAV

It is clear from the research question of the RPDC-GSAV that the collection of comparative data is necessary. Depending on the patient population, the benefit and harm of onasemnogene abeparvovec are to be compared with the benefit and harm of nusinersen or of treatment according to the physician's choice of nusinersen or BSC. Under the restriction of §35a SGB V (3b) to disease-specific data collections without randomization, the following study designs are possible [3]:

- non-randomized comparisons within a study (parallel control) or
- the comparison of single arms of different (single- or multi-arm) studies (parallel or historical control)

The following sections discuss the possibilities of these two study designs for the benefit assessment of onasemnogene abeparvovec versus the appropriate comparator therapy.

Comparison of single arms of different (single- or multi-arm) studies (parallel or historical control)

For the present research questions, it is to be discussed whether the necessary comparison with nusinersen can be conducted using nusinersen arms of already available studies on this drug (historical control).

The comparison of single arms from different studies is fundamentally associated with the problem of a risk of bias due to the use of different data sources. The problem arises, for example, due to a possibly different quality of the data collection or a different definition of data points. In the present therapeutic indication, for example, there are different definitions of permanent ventilation.

The available nusinersen arms from completed studies are primarily from interventional studies in which the treatment regimen was specified by detailed protocols (see Table 8). A potential RPDC-GSAV of the onasemnogene abeparvovec arm would likely be less prescriptive and therefore result in more heterogeneous treatment regimens. These differences can hardly be controlled by adjustment in the analysis.

In addition, for historical controls, patient populations may differ from those prospectively treated with the new drug due to changes in diagnostic and treatment methods. In the case of SMA, the very early initiation of treatment after newborn screening would be an example of a relevant change that has an impact on characteristics of the patient population.

Another challenge of this study design lies in the availability of IPD of the nusinersen arms of studies already completed. For analyses of non-randomized studies for the benefit assessment,

as a rule only confounder adjustment procedures that are performed using IPD are meaningful. The systematic availability of these data for the analysis is unclear.

Irrespective of these methodological considerations, it must be checked whether the potentially available nusinersen arms of completed studies include relevant patient groups, as well as a sufficient number of patients and duration of follow-up, in order to be able to answer the research question of the RPDC-GSAV. For an overview of potentially relevant studies, an exploratory search for studies on nusinersen was conducted in ClinicalTrials.gov and in the EU Clinical Trials Register (search dates 16.09.2020 and 23.09.2020). A total of 24 studies were identified, which are described in Appendix D).

When identifying study arms that would be potentially suitable for comparison with onasemnogene abeparvovec, ongoing and planned observational studies in registries were not considered, as the suitability of registries is assessed separately (see Section 5.3.2).

The assessment of the available nusinersen studies shows that only the studies of the nusinersen development programme of the pharmaceutical company are available for a non-randomized comparison of single arms from different studies (see Appendix D). The following table assigns the available study arms to the patient groups that are potentially relevant for the RPDC-GSAV. A total of 6 studies are involved, excluding the SHINE extension study, which does not recruit any additional patients.

Table 8: Assignment of available nusinersen study arms to relevant patient groups.

	Presymptomatic (≤ 3 copies)			**Symptomatic, type I (≤ 3 copies)**			**Symptomatic, type II (≤ 3 copies)**		**Symptomatic, type III (≤ 3 copies)**	
	1 copy	**2 copies**	**3 copies**	**1 copy**	**2 copies**	**3 copies**	**2 copies**	**3 copies**	**2 copies**	**3 copies**
Study					CS3B (ENDEAR) n = 80 CS3A n = 16 (80% with 2 copies)			CS4 (CHERISH) n = 84 (88% with 3 copies)		
		SM201 (NURTURE) n = 25								
Study SM203 (DEVOTE): 1 arm with approved dosage; number and characteristics of potentially relevant patients unclear. Study SM201 (EMBRACE): 21 patients treated (distribution among different patient groups unclear); children with 5q SMA (homozygous gene deletion or mutation or mixed heterozygosity) without SMA symptoms at birth or within the first week of life and without permanent respiratory support. Start of symptoms at the age of ≤ 6 months with 3 *SMN2* copies or start of symptoms at the age of ≤ 6 months with a screening age of > 7 months with 2 *SMN2* copies or start of symptoms at the age of > 6 months with a screening age of ≤ 18 months with 2 or 3 *SMN2* copies.										

The overview in Table 8 makes it clear that the already available nusinersen study arms cover only part of the relevant patient groups and, moreover, the number of patients included in each case is small. Due to the methodological considerations described above and because of the limited data on nusinersen, the non-randomized comparison of single arms from different studies is not a meaningful approach for the RPDC-GSAV for a benefit assessment of onasemnogene abeparvovec versus nusinersen. Rather, it is also necessary to prospectively collect data on nusinersen for this comparison.

Non-randomized comparisons within a study (parallel control)

The non-randomized comparison of onasemnogene with nusinersen or with a treatment according to the physician's choice within a study (parallel control) avoids the methodological difficulties mentioned in the previous section for the comparison of single arms from different studies.

Since in any case the non-randomized comparison of two drugs has a high risk of bias, the additional potentially biasing factors mentioned above should be avoided. Therefore, under the requirements of §35a (3) SGB V, a non-randomized comparison with a parallel control within one study is recommended for the RPDC-GSAV on onasemnogene abeparvovec.

5.4.1.2 Data sources for the RPDC-GSAV

Primary data source for the RPDC-GSAV

The SMArtCARE registry currently appears to be the most suitable primary data source for a timely RPDC-GSAV (see Section 5.3.2.3.2). The limitations described (collection of data on health-related quality of life, inclusion of patients treated with BSC, source data verification, consideration of potential confounders) should accordingly be considered when planning an RPDC-GSAV, but do not fundamentally counter the suitability of the SMArtCARE registry as a primary data source.

Inclusion of further registries

The RPDC-GSAV can be supported by the inclusion of further (international) registries. The prerequisite for this is that the data collected in the respective registry correspond in scope and quality to the requirements of the RPDC-GSAV and that an analysis can be conducted in accordance with the requirements of the RPDC-GSAV and made available for the benefit assessment. A further prerequisite is that the health care provided in the country in which the data are collected is sufficiently similar to the health care provided in Germany or that the findings obtained from this registry are applicable to the situation in Germany.

Data collection and analysis

For a registry study conducted for an RPDC-GSAV, the starting point for data collection and analysis should be the finalized protocol and the finalized SAP, also for registries that are used as additional data sources.

Whether the data collected in the respective registry meet the requirements for the RPDC-GSAV should be checked by comparing the requirements formulated in the protocol on the registry study with the respective registry protocol. It should also be checked against the general quality criteria for registries (see [3]) whether appropriate steps such as training, plausibility checks and queries support the goal of high-quality quality in the registry. If possible, a source data verification like in the procedure proposed for the SMArtCARE registry (see Section 5.3.2.3.2) should also be performed, if necessary with a smaller sample size.

To facilitate the inclusion of international registries, the transmission of IPD from these registries can be omitted. Instead, the analyses from different registries can be combined meta-analytically [21]. The analysis should be performed for the respective registry using the SAP on the registry study for the RPDC-GSAV. The analysis should address the research question(s) of the RPDC-GSAV (comparison of onasemnogene abeparvovec with the appropriate comparator therapy). The sole provision of follow-up data on individual treatment options (e.g., only on onasemnogene abeparvovec) is not appropriate.

To support the process of data harmonization in both data collection and analysis, it seems useful to also use the Maelstrom Research Guidelines for Rigorous Retrospective Data Harmonization described in Fortier 2017 [22].

Applicability

The analysis by Bladen 2014 showed that relevant differences exist in the care of SMA patients between different countries [17]. This also applies to the comparison of countries with a more developed health care system. In the present therapeutic indication, these differences appear particularly relevant due to the severity of the disease and the associated multimodal treatment approaches. In particular, standards for and the availability of non-drug interventions should be mentioned here, including the provision of remedies and aids, different standards for ventilation (invasive vs. non-invasive), availability of nusinersen and onasemnogene abeparvovec as well as their quality-assured use.

It would therefore be meaningful to describe basic requirements for the care of SMA patients in the protocol on the registry study, derived from existing health care standards in Germany. If major differences exist between these requirements and health care standards in another country, registry data from the other country should not be used; in the case of minor deviations, this could be decided on an outcome basis, if necessary.

The G-BA's planned measure on quality assurance according to §136a (5) SGB V for onasemnogene abeparvovec will name important aspects of health care standards in Germany [4]. After the G-BA's decision on this measure, it should therefore be taken into account in the description of the health care standards.

5.4.2 Duration and scope of the RPDC-GSAV

Duration of the RPDC-GSAV

The duration of the RPDC-GSAV covers 2 aspects. On the one hand, it concerns the duration of follow-up of the individual patients, which should ensure that relevant characteristics in the present therapeutic indication and situation of use, such as the achievable motor development or the individual sustainability of a treatment result, can be evaluated. On the other, it concerns the general duration of data collection in the patient population that is necessary to include or follow up enough patients or events (the sample size required) to collect meaningful data for a quantification of added benefit.

The requirements for these two factors (patient-related duration of follow-up and total duration / sample size) differ for the various research questions to be addressed by the RPDC-GSAV. For example, the question "What level of motor development can be achieved among the treatment alternatives?" can be answered with a shorter individual follow-up period than required for the question "Does the sustainability of this level of development differ among treatment alternatives?" Not least, the importance of certain outcomes differs for the different patient groups, for example, the outcome on mortality and permanent ventilation is of greater importance for patients with SMA type I than for patients with SMA type III. Therefore, for a sufficiently reliable quantification of the added benefit, the necessary duration of data collection should be considered, taking into account the different patient groups as well as different outcomes.

In the following text, considerations on the duration of the RPDC-GSAV are presented on the basis of outcomes on motor development and mortality / permanent ventilation. As currently very few data exist on treatment results with onasemnogene abeparvovec, the relevance of the different scenarios can only be assessed in the course of the regular reviews of the data by the G-BA.

Evaluation of motor development

In the approval studies, both onasemnogene abeparvovec and nusinersen were shown to improve motor development under treatment. In the present clinical picture, the degree of motor development is therefore of particular importance for the planned comparison of onasemnogene abeparvovec and nusinersen. The EMA states that in the onasemnogene abeparvovec CL-303 study, which was considered pivotal for approval, 85% of patients achieved head control, 59% achieved turning from the supine position, and 64% achieved sitting without support at the end of the study (age of the 22 patients: 18 months) [5]. It remains unclear whether and how many of the patients will be able to achieve further motor milestones and how long the milestones achieved will be maintained.

The WHO describes the motor development of infants with 6 milestones, which are passed by healthy children at about 18 months of age (sitting without support to walking without support [23]). Against this background, and taking into account the treatment results of onasemnogene

abeparvovec and nusinersen, the follow-up of patients in the RPDC-GSAV after treatment with onasemnogene abeparvovec up to an age of at least 36 months seems meaningful to investigate how far the motor development of patients with SMA can progress under treatment.

Furthermore, it is relevant how long the achieved level of development is maintained, i.e. how sustainable the treatment result is. To assess the sustainability of the motor development level achieved, follow-up until the age of 5 is suggested (Month 60).

Mortality and permanent ventilation

For patients with severe disease, a combined outcome of mortality and permanent ventilation is particularly relevant. The duration of the RPDC-GSAV for the investigation of a potential added benefit of one of the treatment alternatives based on this combined outcome results from the number of events required for a sufficiently reliable effect estimate; this in turn depends on the event risk, which differs for the different patient populations. An approximation to the number of events required based on the available data from studies on onasemnogene abeparvovec and nusinersen is described below.

Due to potentially unknown confounders, a conclusion on the benefit or harm of an intervention should only be derived from the effects observed in the study if these effects exceed a certain effect size. A (positive or negative) conclusion on the benefit or harm can be drawn if the confidence interval for the effect observed exceeds or is below a threshold to be defined (test for a shifted null hypothesis). Since for the RPDC-GSAV, the fulfilment of the extensive quality requirements is a prerequisite for examining effects, this threshold value should be well below the value for the "dramatic effect" (relative risk of 5–10 [24]), e.g. in a range of 2–5 for the relative risk (or 0.2–0.5 for mortality-lowering interventions). The specific threshold depends on the quality of the data in the individual case, including knowledge of relevant confounders. Depending on the data, such a threshold can also be applied specifically to outcomes, e.g. due to the lack of blinding of treatments or a different direction of bias for positive or negative effects.

To approximate the appropriate sample size for the RPDC-GSAV, a sample size estimate was performed based on the combined outcome of mortality and permanent ventilation for a comparison of onasemnogene abeparvovec and nusinersen, using the results of the following studies:

- the ENDEAR nusinersen study with a proportion of patients with an event under nusinersen at the end of study (with study duration median, min–max: 280, 6–442 days): n = 31/80 (39%) and
- the onasemnogene abeparvovec study CL-303 with a proportion of patients with an event under nusinersen at the end of study (with study duration > 10.5 months after treatment initiation): n = 2/22 (9.1%).

Assuming very high-quality data and assuming a necessary minimum effect size of about 0.5, the following scenarios emerge:

- Assumptions (for application of the Cox model with a shifted null hypothesis)
  - significance level 5%, power 80%, 2-sided test
  - exponential distribution, censoring only at end of study
  - proportion of patients with an event in the control group (nusinersen) after 280 days: 40%; expected effect hazard ratio (HR) = 0.25
- Sample size scenarios
  - Scenario 1 – calculation based on a follow-up of 280 days
    - Scenario 1a) upper limit of the 95% confidence interval (CI) < 0.5: sample size 2 x 126 = 252 patients (66 events)
    - Scenario 1b) upper limit of 95% CI < 0.4: sample size 2 x 274 = 548 patients (142 events)
  - Scenario 2 – calculation based on a follow-up of 36 months, updating the data from the ENDEAR studies (i.e., proportion of patients with an event in the control group [nusinersen] after 1080 days 86.1%)
    - Scenario 2a) upper limit of 95% CI < 0.5: sample size 2 x 53 = 106 patients (66 events).
    - Scenario 2b) upper limit of 95% CI < 0.4: sample size 2 x 114 = 228 patients (142 events)

Depending on the duration of follow-up and the desired certainty of the effect, the number of patients to be included to examine the mortality / permanent ventilation outcome ranges from 100 to 600 (to observe approximately 60–150 events).

Since the mortality / permanent ventilation outcome is primarily relevant for patients with SMA type I, the required sample size would have to be achieved in this subpopulation. In contrast, for patients with less severe disease, primarily motor development is relevant. Insufficient data are available for a sample size estimate based on motor development outcomes (e.g., on the achievement of the different WHO motor development milestones after 36 months). In summary, therefore only a rough estimate can initially be proposed for a sample size for the RPDC-GSAV. Based on the considerations described above, the inclusion and follow-up of approximately 500 patients is therefore proposed. The informative value of the data collected for this sample size will also depend on the distribution of patients among the treatment groups. Due to the great uncertainty of the estimation of an adequate sample size, a review of the assumptions in the course of data collection is recommended so that the sample size can be adjusted, if necessary. The corresponding procedures required should be described in the study protocol. This review of the sample size should also take into account other factors, such as the

sample sizes required for the planned adjustment procedures or the drop-out of patients from follow-up.

Scope of the RPDC-GSAV

The scope of the RPDC-GSAV results from the outcomes to be documented (see PICO in Section 5.2), the sample size to be followed up (recommendation: approx. 500 patients) and the recommended duration of follow-up (recommendation: 36 months for the assessment of motor development, 60 months for the sustainability of treatment effects).

5.4.3 Data analysis

Rapid report A19-43[17] describes the general requirements for the analysis of comparative studies without randomization [3].

Development of a statistical analysis plan (SAP)

The planning of the analysis for such studies and thus also for the registry study for the RPDC-GSAV on onasemnogene abeparvovec should correspond to the planning of the analysis of comparative studies with randomization [25]. This includes an SAP, which is defined in advance, and should in particular include:

- which statistical methods and models are used
- which methods and criteria are used for model selection and adaptation
- to what extent and for what reasons missing data can be expected
- which measures are taken to avoid missing data
- which analysis strategies are chosen to handle missing data
- how implausible data and outliers are dealt with, and
- which sensitivity analyses are used to check the robustness of the results.

General requirements for confounder adjustment

A key aspect in comparative studies without randomization is therefore the adequate adjustment for confounders in order to obtain interpretable estimates of the effect of interest. In order to achieve adequate confounder control, regardless of the methods used, it is particularly necessary to [26-28]

- identify in advance all important confounders (including important interactions) and consider them in the model in an appropriate form
- completely collect data on these important confounders in the study

[17] "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)"

- plan the study with a sufficient sample size to be able to consider all confounders in the model
- describe the causal model exactly, e.g. by means of causal graphics
- present the assumptions of the causal model, and
- substantiate, e.g. on the basis of scientific literature, why these assumptions can be justified in the specific case of use.

If one or more of these important confounders are not contained in the data set, they should be supplemented, as otherwise the analysis results are potentially not suitable for a benefit assessment. As described in Section 5.3.2.3.2 on the limitations of the SMArtCARE registry, confounders relevant for the research questions of the RPDC-GSAV must be identified in advance during the development of the protocol and SAP of the registry study by means of a literature search with the involvement of experts [3].

The minimum sample size required, as indicated above, also depends on the number of confounders to be adjusted for in the model. As guidance, in the literature at least 10 persons per confounder are required for regression analyses for continuous data [29], and at least 10 events per confounder for binary data and survival time analyses [30]. Based on the sample size calculation described in Section 5.4.2 and the event rate used as a basis there, it can probably be assumed that this requirement is fulfilled with the sample size described there for the registry study. However, this should be verified during the development of the protocol and the SAP.

Methodological approaches to confounder adjustment

Of the methodological approaches described in rapid report A19-43, the propensity score method appears to be the most suitable for confounder adjustment in the present case due to the properties described in A19-43. Among other things, the aspects of positivity, overlap and balance must be taken into account [3].

- For positivity, the inclusion criteria of the registry study for all patients must include the requirements of use for both onasemnogene abeparvovec and nusinersen, because this is the minimum requirement for both treatment options to represent a potential treatment option at the time of the treatment decision.
- The degree of overlap and balance between the groups depends first of all on the model chosen to form the propensity score. However, it can also be influenced by “trimming” (excluding patients in non-overlapping areas of the propensity score) and the adjustment methods. The sufficiently overlapping and sufficiently balanced patient population is ultimately the population for whom the estimated effects apply using the propensity score. Therefore, this population should be described in detail and it should be investigated whether it sufficiently depicts the population selected for the original research question.
- Which method is the most suitable for a particular case of use can sometimes only be decided on the basis of the specific data, since different methods can lead to different

degrees of overlap or balance [31]. However, the SAP can and should describe the decision-making structure for method selection. This includes, for example, the necessary minimum degree of overlap and balance. In addition, sensitivity analyses should be conducted with different propensity score methods, provided that these also fulfil the necessary minimum degree of overlap and balance.

Consideration of historical data on nusinersen

Nusinersen was approved some years before onasemnogene abeparvovec. Therefore, until the approval of onasemnogene abeparvovec, only nusinersen was available among the agents to be considered in the RPDC-GSAV. It is an open question as to whether patients treated with nusinersen prior to the approval of onasemnogene abeparvovec would have been more likely to be treated with onasemnogene abeparvovec if it had been available earlier.

If the data on nusinersen collected prior to the approval of onasemnogene abeparvovec can in principle be used due to the availability and quality of the data (see comments on the SMArtCARE registry in Section 5.3.2.3.2), it would appear meaningful to perform analyses with and without consideration of such data on nusinersen. From this, it may also be possible to derive indications as to which criteria influence the choice between onasemnogene abeparvovec and nusinersen.

BSC as part of the appropriate comparator therapy for research question 2 (SMA type III)

The appropriate comparator therapy for research question 2 of the RPDC-GSAV (SMA type III) is treatment according to the physician's choice of nusinersen or BSC. Should a general newborn screening for SMA be introduced in Germany, it can be assumed that the available agents for targeted SMA therapy will already increasingly be used presymptomatically. This would be associated with a decreasing prevalence of patients with SMA type III who were or are not treated with such agents but with BSC. Therefore, it seems meaningful that the comparison with BSC for patients with SMA type III is not the focus of the RPDC-GSAV. For research question 2, it is therefore recommended to perform analyses primarily for the comparison with nusinersen and therefore both with and without inclusion of patients treated with BSC.

Interim analyses

For several reasons, SMA is currently a very dynamic therapeutic indication. These include the recent approval of targeted therapies, but also the national and international discussion on the introduction of newborn screening for SMA. The latter will potentially markedly bring forward treatment initiation. And because of the longer survival of children, motor development may become even more important in the comparative assessment of treatment options. Moreover, as shown in the previous sections in Table 6 und Table 8, knowledge of the effects of onasemnogene abeparvovec and nusinersen is limited.

For the RPDC-GSAV, this means that it should react to substantial changes in the evidence available. This could include, in particular, an adjustment of the sample size required or an adjustment of the necessary follow-up period.

It is therefore recommended to perform regular, preplanned interim analyses and to discuss their consequences for the ongoing RPDC-GSAV, for example, with regard to sample size and follow-up period.

Merging the results from different registries

As described in Section 5.4.1.2, the protocol and SAP for the registry study on the RPDC-GSAV should be the starting point for the inclusion of other registries. The analysis can be performed separately for each registry, and joint analysis is possible as a meta-analysis of the individual registry results.

The principles described in this Section 5.4.3 apply equally to the analysis within the respective registry.

6 Discussion

The present concept for the RPDC-GSAV on onasemnogene abeparvovec was developed within the first procedure for the implementation of §35a SGB V in the G-BA. It maps the research question in 2 PICOs and contains recommendations on the type, duration and scope of data collection as well as on data analysis and further methodological aspects.

One component in the development of the concept was to examine the ongoing and planned data collections on onasemnogene abeparvovec, which result from requirements of regulatory and other approval authorities. The aim is to clarify to what extent the research question of the data collection can be answered (also in the short term) with the help of these studies. In the present case, this examination has shown that the studies stipulated are not suitable for generating the data needed to quantify the added benefit of onasemnogene abeparvovec versus the appropriate comparator therapy (see Section 5.3.1). The reason for this is presumably the different research questions of the approval process and the benefit assessment. In this judgement, it should be taken into account that the information on the registry stipulated by the regulatory authorities (RESTORE registry) was insufficient to assess the data collected for the regulatory authorities. However, the information available in the literature on this registry [15] suggests that the registry in its current form cannot provide data to sufficiently address the research questions of the benefit assessment (see Section 5.3.2.3.2).

An important instrument for an RPDC-GSAV are disease registries, in which data collection can be conducted as a registry study. In order for the data collected to contribute to the quantification of added benefit in a benefit assessment, the registries and the data collected must fulfil certain quality criteria [3]. Identifying and assessing existing SMA registries is therefore an important component in this report. After identifying potentially relevant registries, registry operators were contacted to request detailed information for the assessment of the registries. This information was provided by the operators of the TREAT-NMD SMA registry and the SMArtCARE registry and contributed markedly to the assessment of the registries. It is therefore regrettable that the parties responsible for the RESTORE registry did not provide the information on the registry, despite a request. According to information in ClinicalTrials.gov, UBC/AveXis was responsible until 15 September 2020, and Novartis Gene Therapies has been responsible since 16 September 2020 [10]. This information gap could not be filled from publicly available documents, as no registry protocol is publicly available for the RESTORE registry even 2 years after the start of the study (study start date according to ClinicalTrials.gov September 2018 [10]).

The duration and scope of the RPDC-GSAV is ideally derived from a sample size estimate. In the present case, the sample size required can only be approximated, as robust data that could form the basis of a sample size estimate are missing. In particular, it is relevant that for parts of the patient population (e.g. for patients with SMA type II or III) only very few data are available for both onasemnogene abeparvovec and the appropriate comparator therapy nusinersen. During the course of data collection, it will therefore be necessary to examine whether

adjustments to data collection will result from the information then available, for example, with regard to the sample size required or duration of patient follow-up. The legal regulations also provide for such an examination.

7 Conclusion

The concept for an RPDC-GSAV on onasemnogene abeparvovec has the following components:

PICO

Table 9: PICO patient group A for the RPDC-GSAV

P(opulation)	▪ Presymptomatic patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene as well as ▪ Symptomatic patients with 5q SMA type I and II with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.
I(ntervention)	Onasemnogene abeparvovec
C(omparator)	Nusinersen
O(outcome)	Mortality ▪ deaths Morbidity ▪ motor function (recorded with age-appropriate instruments, depending on disease severity, especially achievement of WHO motor development milestones) ▪ respiratory function (need for [permanent] ventilation) ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) ▪ further complications of the disease (e.g. pain, orthopaedic complications) Adverse effects ▪ adverse events Health-related quality of life ▪ health-related quality of life (recorded with an age-appropriate instrument)
RPDC-GSAV: routine practice data collection according to the “Gesetz für mehr Sicherheit in der Arzneimittelversorgung” (Law for More Safety in the Supply of Medicines); SMA: spinal muscular atrophy; SMN: survival motor neuron; WHO: World Health Organization	

Table 10: PICO patient group B for the RPDC-GSAV

P(opulation)	▪ Symptomatic patients with 5q SMA type III with a bi-allelic mutation in the *SMN* 1 gene and up to 3 copies of the *SMN2* gene
I(ntervention)	Onasemnogene abeparvovec
C(omparator)	Treatment according to the physician's choice of nusinersen or BSC
O(outcome)	Mortality ▪ deaths Morbidity ▪ motor function (assessed with age-appropriate instruments, depending on disease severity, especially achievement of WHO motor development milestones) ▪ respiratory function (need for [permanent] ventilation) ▪ bulbar function (ability to swallow and speak, need for non-oral nutritional support) ▪ further complications of the disease (e.g. pain, orthopaedic complications) Adverse effects ▪ adverse events Health-related quality of life ▪ health-related quality of life (recorded with an age-appropriate instrument)
BSC: best supportive care; RPDC-GSAV: routine practice data collection according to the "Gesetz für mehr Sicherheit in der Arzneimittelversorgung" (Law for More Safety in the Supply of Medicines); SMA: spinal muscular atrophy; SMN: survival motor neuron; WHO: World Health Organization	

Type and methods of data collection

- Non-randomized comparison of onasemnogene abeparvovec with the appropriate comparator therapy in a study (parallel control); study protocol and SAP with emulation of the target trial
- Conduct of the studies in a disease registry, currently suitable: SMArtCARE (inclusion of other registries possible under certain conditions)

Duration and scope of data collection

- Duration determined by the necessary follow-up period per patient and the sample size required
  - follow-up of achievable motor development: until Month 36
  - follow-up of the sustainability of the achieved development: until Month 60
  - sample size: exploratory sample size estimate based on the outcome of mortality / permanent ventilation (about 500 patients)
- Scope determined by the outcomes to be recorded and the sample size required

Analysis of data collection

- Examination of the assumptions for the duration and scope of the RPDC-GSAV in the course of data collection; adjustment of planning if necessary
- Analysis with adequate, sufficiently prespecified confounder adjustment (according to Section 5.4.3)

References

1. Bundesministerium für Gesundheit. Gesetz für mehr Sicherheit in der Arzneimittelversorgung. Bundesgesetzblatt Teil I 2019; (30): 1202-1220.

2. SGB V Handbuch: Sozialgesetzbuch V; Krankenversicherung. Altötting: KKF-Verlag; 2020.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Konzepte zur Generierung versorgungsnaher Daten und deren Auswertung zum Zwecke der Nutzenbewertung von Arzneimitteln nach § 35a SGB V: Rapid Report; Auftrag A19-43; Version 1.1 [online]. 13.05.2020 [Accessed: 02.06.2020]. URL: https://www.iqwig.de/download/A19-43_Versorgungsnahe-Daten-zum-Zwecke-der-Nutzenbewertung_Rapid-Report_V1-1.pdf.

4. Gemeinsamer Bundesausschuss. Maßnahmen zur Qualitätssicherung nach § 136a Absatz 5 SGB V: Einleitung eines Stellungnahmeverfahrens; Onasemnogene abeparvovec bei spinaler Muskelatrophie [online]. [Accessed: 15.08.2020]. URL: https://www.g-ba.de/beschluesse/4414/.

5. European Medicines Agency. Zolgensma: European public assessment report [online]. 26.03.2020 [Accessed: 16.09.2020]. URL: https://www.ema.europa.eu/documents/assessment-report/zolgensma-epar-public-assessment-report_en.pdf.

6. European Medicines Agency. Summary of risk management plan for Zolgensma (onasemnogene abeparvovec) [online]. 27.05.2020 [Accessed: 16.09.2020]. URL: https://www.ema.europa.eu/documents/rmp-summary/zolgensma-epar-risk-management-plan-summary_en.pdf.

7. Food and Drug Administration. Zolgensma: application number 125694/0; BLA clinical review memorandum [online]. 23.05.2019 [Accessed: 16.09.2020]. URL: https://www.fda.gov/media/128116/download.

8. Food and Drug Administration. Zolgensma: application number 125694/0; pharmacovigilance plan review memorandum [online]. 01.06.2019 [Accessed: 16.09.2020]. URL: https://www.fda.gov/media/128116/download.

9. AveXis. Gene replacement therapy clinical trial for participants with spinal muscular atrophy type 1 (STR1VE): study details [online]. 16.07.2020 [Accessed: 10.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03306277.

10. AveXis. Registry of patients with a diagnosis of spinal muscular atrophy (SMA): study details [online]. 18.09.2020 [Accessed: 20.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04174157.

11. AveXis. Single-dose gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1 (STRIVE-EU): study details [online]. 09.03.2020 [Accessed: 10.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03461289.

12. AveXis. Pre-symptomatic study of intravenous onasemnogene abeparvovec-xioi in spinal muscular atrophy (SMA) for patients with multiple copies of SMN2 (SPR1NT) [online]. 18.05.2020 [Accessed: 10.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03505099.

13. AveXis. Long-term follow-up study for patients from AVXS-101-CL-101 (START) [online]. 28.08.2020 [Accessed: 10.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03421977.

14. AveXis. Long-term follow-up study of patients receiving onasemnogene abeparvovec-xioi: study details [online]. 24.08.2020 [Accessed: 10.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04042025.

15. Finkel RS, Day JW, De Vivo DC et al. RESTORE: a prospective multinational registry of patients with genetically confirmed spinal muscular atrophy; rationale and study design. J Neuromuscul Dis 2020; 7(2): 145-152. https://dx.doi.org/10.3233/JND-190451.

16. Pechmann A, Konig K, Bernert G et al. SMArtCARE: a platform to collect real-life outcome data of patients with spinal muscular atrophy. Orphanet J Rare Dis 2019; 14: 18. https://dx.doi.org/10.1186/s13023-019-0998-4.

17. Bladen CL, Thompson R, Jackson JM et al. Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe. J Neurol 2014; 261(1): 152-163. https://dx.doi.org/10.1007/s00415-013-7154-1.

18. Konig K, Pechmann A, Thiele S et al. De-duplicating patient records from three independent data sources reveals the incidence of rare neuromuscular disorders in Germany. Orphanet J Rare Dis 2019; 14: 152. https://dx.doi.org/10.1186/s13023-019-1125-2.

19. Verhaart IEC, Robertson A, Leary R et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol 2017; 264(7): 1465-1473. https://dx.doi.org/10.1007/s00415-017-8549-1.

20. TREAT-NMD. Core dataset for spinal muscular atrophy (SMA) [online]. [Accessed: 27.7.2020]. URL: https://treat-nmd.org/patient-registries/treat-nmd-core-datasets/sma-core-dataset/.

21. Scotti L, Rea F, Corrao G. One-stage and two-stage meta-analysis of individual participant data led to consistent summarized evidence: lessons learned from combining multiple databases. J Clin Epidemiol 2018; 95: 19-27. https://dx.doi.org/10.1016/j.jclinepi.2017.11.020.

22. Fortier I, Raina P, Van den Heuvel ER et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. Int J Epidemiol 2017; 46(1): 103-105. https://dx.doi.org/10.1093/ije/dyw075.

23. WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: windows of achievement for six gross motor development milestones. Acta Paediatr Suppl 2006; 95(S450): 86-95. https://dx.doi.org/10.1111/j.1651-2227.2006.tb02379.x.

24. Glasziou PP, Chalmers I, Rawlins M et al. When are randomised trials unnecessary? Picking signal from noise. BMJ 2007; 334(7589): 349-351.

25. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. Stat Med 2007; 26(1): 20-36. https://dx.doi.org/10.1002/sim.2739.

26. Berger ML, Mamdani M, Atkins D et al. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources; the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report; part I. Value Health 2009; 12(8): 1044-1052. https://dx.doi.org/10.1111/j.1524-4733.2009.00600.x.

27. Cox E, Martin BC, Van Staa T et al. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources; the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report; part II. Value Health 2009; 12(8): 1053-1061. https://dx.doi.org/10.1111/j.1524-4733.2009.00601.x.

28. Johnson ML, Crown W, Martin BC et al. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources; the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report; part III. Value Health 2009; 12(8): 1062-1073. https://dx.doi.org/10.1111/j.1524-4733.2009.00602.x.

29. Harrell FE Jr. Regression modelling strategies: with applications to linear models, logistic regression, and survival analysis. New York: Springer; 2001.

30. Peduzzi P, Concato J, Kemper E et al. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49(12): 1373-1379. https://dx.doi.org/10.1016/s0895-4356(96)00236-3.

31. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ 2019; 367: l5657. https://dx.doi.org/10.1136/bmj.l5657.

32. Biogen. A study of nusinersen among participants with spinal muscular atrophy who received onasemnogene abeparvovec-xioi: study details [online]. 27.07.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04488133.

33. Northwell Health. Effect of nusinersen on adults with spinal muscular atrophy: study details [online]. 28.02.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03878030.

34. NYU Langone Health. Pulmonary function test changes and respiratory muscle strength trends in spinal muscular atrophy patients receiving nusinersen treatments: study details [online]. 07.08.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04050852.

35. Biogen. Non-interventional, postmarketing surveillance study of nusinersen sodium injection (PANDA): study details [online]. 18.08.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04419233.

36. Biogen. Observational, postmarketing surveillance study of spinraza injection (nusinersen sodium): study details [online]. 11.06.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04317794.

37. Biogen. An open-label safety and tolerability study of nusinersen (ISIS 396443) in participants with spinal muscular atrophy (SMA) who previously participated in ISIS 396443-CS2 (NCT01703988) or ISIS 396443-CS10 (NCT01780246): study details [online]. 24.03.2017 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02052791.

38. Biogen. A study of multiple doses of nusinersen (ISIS 396443) delivered to infants with genetically diagnosed and presymptomatic spinal muscular atrophy (NURTURE): study details [online]. 03.12.2019 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02386553.

39. Biogen. An open-label safety, tolerability and dose-range finding study of multiple doses of nusinersen (ISIS 396443) in participants with spinal muscular atrophy: study details [online]. 13.03.2017 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT01703988.

40. Biogen. An open-label safety, tolerability and dose-range finding study of multiple doses of nusinersen (ISIS 396443) in participants with spinal muscular atrophy: study results [online]. 13.03.2017 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01703988.

41. Biogen. An open-label safety and tolerability study of nusinersen (ISIS 396443) in participants with spinal muscular atrophy WHO previously participated in ISIS 396443-CS1 (NCT01494701): study details [online]. 04.04.2017 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT01780246.

42. Biogen. A study to assess the efficacy, safety and pharmacokinetics of nusinersen (ISIS 396443) in infants with spinal muscular atrophy (SMA): study details [online]. 30.10.2018 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT01839656.

43. Biogen. A study to assess the efficacy, safety and pharmacokinetics of nusinersen (ISIS 396443) in infants with spinal muscular atrophy (SMA): study results [online]. 30.10.2018 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01839656.

44. Biogen. A study to assess the efficacy and safety of nusinersen (ISIS 396443) in participants with later-onset spinal muscular atrophy (SMA) (CHERISH): study details [online]. 22.02.2018 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02292537.

45. Biogen. A study to assess the efficacy and safety of nusinersen (ISIS 396443) in participants with later-onset spinal muscular atrophy (SMA) (CHERISH): study results [online]. 22.02.2018 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02292537.

46. Biogen. Expanded access program (EAP) for nusinersen in participants with infantile-onset (Consistent With Type 1) spinal muscular atrophy (SMA): study details [online]. 29.04.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02865109.

47. Biogen. Study of nusinersen (BIIB058) in participants with spinal muscular atrophy (DEVOTE): study details [online]. 09.07.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04089566.

48. Biogen. A study for participants with spinal muscular atrophy (SMA) WHO previously participated in nusinersen (ISIS 396443) investigational studies: (SHINE); study details [online]. 14.04.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02594124.

49. Biogen. A study to assess the safety and tolerability of nusinersen (ISIS 396443) in participants with spinal muscular atrophy (SMA): (EMBRACE); study details [online]. 27.01.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02462759.

50. Biogen. A study to assess the safety and tolerability of nusinersen (ISIS 396443) in participants with spinal muscular atrophy (SMA): (EMBRACE); study results [online]. 27.01.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02462759.

51. Biogen. A study to assess the efficacy and safety of nusinersen (ISIS 396443) in infants with spinal muscular atrophy (ENDEAR): study details [online]. 28.07.2017 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT02193074.

52. Biogen. A study to assess the efficacy and safety of nusinersen (ISIS 396443) in infants with spinal muscular atrophy (ENDEAR): study results [online]. 28.07.2017 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02193074.

53. Washington University School of Medicine. Spinraza in adult spinal muscular atrophy (SAS): study details [online]. 11.08.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03709784.

54. Biogen. An open-label safety, tolerability, and dose-range finding study of nusinersen (ISIS 396443) in participants with spinal muscular atrophy (SMA) (SMNRx): study details [online]. 06.04.2017 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT01494701.

55. Hospital Israelita Albert Einstein. Characterization of the clinical-epidemiological profile of patients with SMA5q types II and III: observational study; study details [online]. 01.06.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04404764.

56. Centre Hospitalier Universitaire de Nice. Monitoring to the evolution of motor function in SMA type II adults patients treated with Spinraza (SMAII): study details [online]. 12.11.2019 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04159987.

57. Ohio State University. Motor unit number estimation (MUNE) in adults with spinal muscular atrophy (SMA): study details [online]. 28.10.2019 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04139343.

58. Hoffmann-La Roche. A study of risdiplam (RO7034067) in adult and pediatric participants with spinal muscular atrophy (Jewelfish): study details [online]. 21.07.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03032172.

59. Institut de Myologie. European registry of patients with infantile-onset spinal muscular atrophy: study details [online]. 24.01.2018 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03339830.

60. Assistance Publique - Hôpitaux de Paris. French register of patients with spinal muscular atrophy (SMA): study details [online]. 05.02.2020 [Accessed: 22.09.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT04177134.

Appendix A Search strategies for searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL <1946 to July 27, 2020>

#	Searches
1	exp Muscular Atrophy, Spinal/
2	spinal muscular atroph*.ti,ab.
3	or/1-2
4	exp Registries/
5	regist*.ti,ab.
6	or/4-5
7	3 and 6

Appendix B Responses from registry operators

B.1 Response from the RESTORE registry

For the RESTORE registry no response is available despite a request.

B.2 Response from the SMArtCARE registry

The completed (German-language) questionnaire submitted by the SMArtCARE registry is presented below (the questionnaire and responses were translated by IQWiG).

Part 1: Data included in the registry

1. Who enters data into the registry? (multiple answer possible)

☐ Patient/relative ☒ Doctor/therapist ☐ Documentation assistant

If you ticked more than one answer, please provide a short explanation:

Currently, data entry is carried out exclusively by the treatment centres. A patient portal is planned with which patients can directly access a selection of their own data (read-only) and questionnaires can be posted, which can then be completed online by patients or relatives. A test version is already available and will go live in 2020.

2. Which data on genetic findings are documented in the registry (e.g. genetic identification procedure, date, SMA type, technique applied to determine number of *SMN2* copies, number of *SMN2* copies)?

Mutation type in *SMN1*, number of *SMN2* copies, date of genetic finding, name of genetic institute, technique used to determine number of *SMN2* copies

Reference to document, if applicable:

Excel file Data Dictionary (sheet: Registration_Baseline, lines 18-26)

3. Which parameters are used in the registry to determine the patients' course of disease (e.g. motor development, respiratory and nutritional status)?

The application of the various parameters depends on the age, functional status and, if applicable, treatment of the patients. There are recommendations on time intervals and parameters for the treatment centres. The database suggests the next visit date and the recommended parameters according to these logarithms. Time intervals and tools are largely identical for the treatments (nusinersen, Zolgensma, risdiplam), so that a possible comparison is facilitated.

Motor development: WHO motor milestones, HINE-2, CHOP INTEND, HFMSE, RULM, 6-MWT

Respiratory situation: pulmonary function testing, use of respiratory support, type of respiratory support, duration of use, type of secretion management

Feeding situation: weight, need for tube feeding, question about difficulty swallowing or chewing

Reference to document:

Recommendations on examinations see pdf file:
SMArtCARE_Uebersicht_Verlaufbeobachtung_SMArtCARE_V5.0_20200812,
Details see DataDictionary (especially sheet: Medical Assessment)

4. **Please specify in detail the information collected on the criterion "ventilation". Please address in particular the aspects of time of initiation and type of ventilation, local treatment options, and local decision criteria for ventilation.**

Type of respiratory support, start/end date of ventilation, hours of ventilation, frequency of use (daily, occasionally, only in acute infection), time of use, secretion management. A standardized recording of the decision criteria for/against ventilation does not seem possible or meaningful to us, as it often depends on a subjective clinical assessment.

Reference to document, if applicable:

Details see DataDictionary (sheet: Medical assessment, lines 7-33)

5. **Which standardized procedures or measurement tools/scales do you use to document the course of disease in patients with clinically diagnosed SMA type 1 or with up to 3 copies of the *SMN2* gene?**

See answer to Question 3. The choice of measurement tools is not directly dependent on SMA type or number of *SMN2* copies, but on age and functional status. For the individual measurement tools, not only the total scores but all items are recorded.

☒ CHOP-INTEND score (Children´s Hospital of Philadelphia Infant Test of Neuromuscular Disorders)

☒ HFMS score (Hammersmith Functional Motor Scale)

☒ HFMS-E score (Hammersmith Functional Motor Scale - Expanded)

☒ HINE score (Hammersmith Infant Neurological Examination), Section 2

☒ Observed WHO score (World Health Organization Motor Development Milestones)

Do you use any other validated measurement tools to document the course of disease **in the target groups named above**?

RULM, 6-MWT, Neurophysiology (optional, only in some centres)

Reference to document: DataDictionary

6. Which standardized measurement tools for determining health-related quality of life do you use as a third-party assessment (affected children) or a self-assessment (parents/other carers)?

There is still no clear consensus on which quality of life tools (third-party and self-assessment) are valid and sensitive in SMA. So far, experiences in clinical trials are very heterogeneous. Therefore, the Steering Committee has not yet recommended a tool in this regard. Currently, the use of the SMAIS test developed by Roche is under discussion.

Up to now, we only ask patients or relatives about "general condition", "motor function and respiratory function". Improvement or deterioration can be indicated on a 5-point scale. Reference time frame is 3 months in the first year of life, 6 months < age 12, and 1 year > age 12.

Reference to document:

DataDictionary (sheet: Medical Assessment, lines 181-190)

7. Which data do you collect in the registry as potential "confounders" (e.g. duration of disease, indicators of disease severity, number of *SMN2* copies, comorbidity) in order to be able to address the impact of bias in analyses (e.g. of treatment comparisons)?

Duration of disease, number of *SMN2* copies, concomitant diseases, body weight, scoliosis, spinal surgery, contractures, best motor function achieved (before initiation of therapy), and others.

Reference to document: DataDictionary (sheet: Baseline und Medical Assessment)

8. Information for third parties (e.g. the G-BA) with regard to the reproducibility of the analysis:

☐ only aggregate results data are planned

☒ (anonymized) individual patient data sets are available under the following conditions (please briefly explain):

SMArtCARE is a disease-specific registry. To date, funding has been provided by the pharmaceutical industry. The SMArtCARE network has full data sovereignty in this process. For all statistical analyses, a finalized SAP must first be approved by the Steering Committee. Only then will the analyses be performed. It is the goal of the academic network to perform the analyses itself, if possible. It is not intended, for example, to pass on data to pharmaceutical companies, which then perform their own analyses without consultation. It is conceivable that joint analyses with other registries (e.g., international) may be scientifically meaningful. In this case, too, an SAP must be approved in advance by the Steering Committee. Sharing anonymized data is conceivable in principle and covered by patient

consent and the ethics vote, but would have to be discussed in detail in individual cases and approved by the Steering Committee.

Part 2: Quality

9. Is a detailed description available for your registry in terms of a "registry protocol”?

☐ no ☐ yes ☒ yes, see attachment

Reference to document: SMArtCARE_Registry_protocol_Vers1.3_20180511.pdf

10. Are precise definitions and operationalizations available for the exposures, clinical events, outcomes and confounders for which you collect data in your registry?

☐ no ☒ yes

11. Is an up-to-date data set description and/or a coding manual available for your registry?

☐ no ☐ yes ☒ yes, see attachment

12. Do you conduct training on how to collect and record data for your registry?

☐ no ☒ yes

The network usually conducts workshops four times a year for physical therapists, physicians, and study coordinators with training in the outcome measure, data entry, etc. See also www.smartcare.de under continuing education (“Fortbildungen”). In 2020, there was a switch to webinars.

13. Are there clearly defined inclusion and exclusion criteria for the registered patients?

☐ no ☒ yes

The only inclusion criterion is a genetically confirmed 5q SMA and the available consent to participate.

14. Have you implemented measures in the registry to ensure the accuracy of the data and to provide information on error rates (e.g. through source data verification, internal and external audits, IT-based checks [e.g. cross-reference checks])?

☐ no ☒ yes ☐ partially

The electronic Case Report Forms contains various direct data checks. Formats and validity ranges are checked directly during data entry. Mandatory fields and data formats are defined for data entry. In addition, there are simple (cross-)checks that issue warnings directly in the system during data entry. Each data entry and change can be traced back to a specific person.

The checking of data for completeness, consistency and plausibility is partly done by plausibility checks. The checks to be implemented (programmed in SAS) are defined in advance in a query plan. The queries resulting from the plausibility checks are sent to the centres for the examination of the data provided. Queries are answered directly by changing the data.

Source data verification has not yet been performed because there is no budget available for it. In contrast to an AMG study, the study centres are also not obliged to completely archive all source data. Therefore, it should be considered how a quality control at the centres could look like. If necessary, it would also be conceivable to conduct a clinical study on a subpopulation within SMArtCARE.

Reference to document:

Definitions of data fields and entry options in DataDictionary.

15. If you answered "yes" or "partially" to the previous question, could you briefly outline the main results of these checks?

No project-specific audit has taken place to date. Data management and IT for SMArtCARE are carried out by the Clinical Trials Centre of the University Hospital Freiburg. The unit has been certified as a data management centre by the European Clinical Research Infrastructure Network (ECRIN). Details on the certification standard can be found at https://ecrin.org/data-certification-standards

16. Are changes in processes and definitions systematically documented in your registry ("documentation trail")?

☐ no ☒ yes ☐ partially

The processes in data management and biometric analyses are controlled via a QM system and standard operating procedures. Project-specific changes are documented. All documents are provided with a version number and date.

17. How is the scientific independence of the registry ensured?

See also Question 8. The SMArtCARE Registry is funded by pharmaceutical companies because public funding was not possible. So far, Biogen is the only sponsor. There have been joint conferences with Biogen, Avexis/Novartis, and Roche. Joint funding has been promised by all three. Concrete contract negotiations are already underway with Avexis.

Participating centres will receive an expense allowance per documented visit. The compensation is independent of a possible therapy. Data sovereignty lies with the SMArtCARE network. Statistical analysis plans are prepared by the Institute for Medical Biometry in Freiburg. All SAPs must be approved by the Steering Committee. No data transfer to pharmaceutical companies is foreseen, except when required for regulatory purposes and then only used for these. Joint scientific analyses with registries in other countries are envisioned. Again, the project and SAP must be approved in advance by the Steering Committee in each case. Network participants can propose projects and analyses, which are then discussed by the Steering Committee.

18. Is the funding of your registry secured in the medium term (4-6 years)?

☐ no ☒ yes ☐ unclear

19. Do you use exact dates for patients, diseases and events in the registry data sets?

☐ no ☒ yes ☒ partially (please briefly explain):

Reference to document: DataDictionary

20. Does the registry contain detailed information on drug therapy (active substance, dose, dose change, including dates)?

☐ no ☒ yes ☐ partially (please briefly explain):

No dosages are requested for nusinersen because it is a standard dose (12 mg per administration). Therapy with Zolgensma and risdiplam are not yet included in the DataDictionary. However, paper CRFs already exist that are currently being programmed into the database.

Reference to document: DataDictionary (sheet: nusinersen), PDF versions of the CRFs for Zolgensma

21. Are adverse events in patients recorded systematically, including specific adverse events related to treatment with nusinersen and onasemnogene abeparvovec/dexamethasone?

☐ no ☒ yes ☐ partially (please briefly explain):

Adverse events are actively inquired about during each documented visit.

Reference to document: DataDictionary (sheet: Adverse Event, CRFs for Zolgensma)

22. Are adverse events recorded using the standard terminology MedDRA?

☒ no ☒ yes

23. Do you collect data on the comorbidities of registered patients?

☐ no ☐ yes ☒ yes, with ICD 10 codes

24. In the current structure of your registry, how quickly can the required analyses of data or anonymized individual patient data sets be made available for analysis by third parties?

Within _2__ months

25. Does your registry have the technical and organizational flexibility to implement data set expansions (e.g. additional data collection dates and/or additional measurement tools for specific analysis purposes) within a shorter period of time?

☐ no ☐ yes ☒ yes, under certain conditions (please briefly explain):

Data collection dates can be set as desired, as the date of the visit is flexible. Additional data collection tools can be added. This is possible very promptly via a paper CRF (currently already for Zolgensma). The technical implementation in the eCRF takes a little longer, the transfer from the paper CRF to the database can then be done later.

It should be noted, however, that so far this is a non-interventional collection of real-world data. Thus, only routine clinical data are collected. Therefore, it has to be checked for each new tool whether it represents clinical routine or whether the border to an interventional study is crossed. This might require an extension of the informed consent and ethics vote.

and with the following deadline: paper CRF 1 month, eCRF 4 months, ethics vote and consent 12 months.

26. How do you rate the completeness of the data on children with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene in terms of losses to follow-up or dropouts?

☐ very good ☒ good ☐ average ☐ sufficient ☐ poor ☐ very poor

Please briefly explain your opinion: Almost all paediatric neuromuscular centres participate in the registry. There is a high scientific and clinical interest in generating further data on efficacy and safety. If no data are entered for an extended period of time, the reason will be inquired (see CRF

End of Data Collection). Expense reimbursement for centres is another incentive for regular documentation. The recommendations for evaluation and the CRFs are helpful tools for clinical routine.

27. How do you rate the completeness of the individual data sets generated at each data collection time for children with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene?

☐ very good ☒ good ☐ average ☐ sufficient ☐ poor ☐ very poor

Please briefly explain your opinion: Particularly in paediatric centres, standardized therapy evaluation at neuromuscular centres is usually part of routine clinical practice.

28. How do you rate the accuracy of the data collected for the subgroup of children with SMA described above?

☐ very good ☒ good ☐ average ☐ sufficient ☐ poor ☐ very poor

Please briefly explain your opinion: Physical therapists are well trained through regular trainings. Motor milestones are certainly more robust than exact CHOP-INTEND scores. We plan to introduce certification for assessors. Then, if necessary, data could be filtered to use only data from certified individuals.

29. How do you rate the consistency over time of the data collected in your registry for children with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene?

☐ very good ☒ good ☐ average ☐ sufficient ☐ poor ☐ very poor

Please briefly explain your opinion: See response to Question 28.

30. From a quality point of view, are there filter options for the data sets in your registry, e.g. according to participating centres or the type of persons entering data (doctors, patients/parents)?

☐ no ☒ yes

Part 3: Registered patients

31. Does your registry include patients from Germany with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene and if so, how many?

☐ no ☒ yes _____ (number of patients), included since the year _____

Data export July 1, 2020 (registered patients n=654):

130 patients with SMA type 1, of whom 115 had up to 3 *SMN2* copies.

382 patients with up to 3 *SMN2* copies, thereof 267 not SMA type 1.

Further increase is expected because not all patients documented on paper CRF at the centres have been entered into the database yet. For example, approximately 100 additional patients have been entered in the last two months (07-08/2020).

32. In your opinion, are the data in your registry representative of children from Germany with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene?

☐ no ☒ yes ☐ unclear

Please briefly explain your opinion: The care of these patients is centralized and takes place mainly at the participating hospitals. According to information from the centres and our own experience, the number of patients who refuse to participate in a study is low.

33. Does your registry include patients from Germany with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene who have not received treatment with nusinersen or onasemnogene abeparvovec?

☒ no ☐ yes _____ (number of patients)

If you answered "yes", are the data collected from untreated children consistent with those of treated children?

☐ no ☐ yes

34. Have you implemented an effective procedure to avoid double or multiple registrations of patients in your registry?

☐ no ☒ yes (please briefly explain):

Through data management, it is possible to transfer a patient from one centre to another if the patient agrees. Separate from the clinical data, identifying data is collected in encrypted form. These

are not accessible to data management, but can be used to generate so-called "unique identifiers" to reliably detect duplicates.

Part 4: Registry-specific questions

35. Is it planned for the registry to use standardized instruments for self-assessment and external assessment of the health-related quality of life of the affected children and / or parents and family caregivers in the future? If applicable, which instruments/scales are these?

See Question 6: The technical prerequisites are being created to allow patients to directly fill in questionnaires online. We expect this to improve compliance because the centres do not have to hand out the questionnaires and transfer them to the database.

36. What is the status of the cooperation with the international SMA patient registry RESTORE, which the sponsors of this registry intend according to publications?

Prof. Kirschner is also a member of the Steering Committee of the RESTORE Registry. This is an international, disease-specific SMA registry. The registry is operated by Avexis/Novartis. Primary study sites are located mainly in the USA. In European countries, collaboration with existing registries is planned. Direct recruitment of patients into the RESTORE registry is currently not planned for Germany.

Due to the overall low number of patients, a future international cooperation of the different registries is probably scientifically meaningful. The nature of the collaboration has been concretized in bilateral discussions over the past months. It is not planned that SMArtCARE data will be exported and imported into the RESTORE registry. Rather, it is conceivable to export data from both registries and possibly other registries and analyse them collectively. However, this requires a project plan with an SAP in each case, which must be approved in advance by the SMArtCARE Steering Committee.

B.3 Response from the TREAT-NMD SMA global registry

The completed (English-language) questionnaire submitted by the TREAT-NMD SMA global registry is presented below. Despite a request, separate information on the German SMA registry, Munich, is not available.

Part 1: Data included in the registry

35. Who enters data into the registry? (multiple answer possible)

☒ Patient/relative ☒ Doctor/therapist ☒ Documentation assistant

If you ticked more than one answer, please provide a short explanation:

Due to the federated nature of the TREAT-NMD global registry Network for SMA there are a variety of different data entry models. The main types are clinician-entered, patient-entered, or patient-entered and clinician-verified. In some registries, the clinician-reported data is entered by a Registry Curator or data entry person, following review of clinical notes.

36. Which data on genetic findings are documented in the registry (e.g. genetic identification procedure, date, SMA type, technique applied to determine number of *SMN2* copies, number of *SMN2* copies)?

The following are all included in our v1 SMA dataset, implemented in 2018 and now collected by the majority of our affiliated registries:

- Method, date and location of genetic testing
- *SMN1* mutation name, testing method
- *SMN2* copy number and testing method

The following are proposed to be specified in v2 (*to be confirmed at the end of September, registries already collecting v1 will be asked to implement applicable changes within 6 months*):

- *SMN1* variant (incl HGVS)
- *SMN1* testing method
- SNM2 copy number
- *SMN2* copy number testing method
- *SMN2* variant c.859G>C
- *SMN2* variant c.859G>C testing method

Reference to document, if applicable:

For v1: See Section 4 (Genetic Diagnosis) https://treat-nmd.org/wp-content/uploads/2019/06/SMA-Full_Expanded_SMA_Core_Dataset.pdf

For v2: https://sma.treat-nmd.org/items/Genetics

37. Which parameters are used in the registry to determine the patients' course of disease (e.g. motor development, respiratory and nutritional status)?

In v1 and v2 we include groups of data items relating to; clinical observations, scoliosis, motor function, wheelchair use, nutrition, pulmonary function, allopathic drug usage, hospitalisations and comorbidities, at least one validated motor outcome measure per patient (in clinician-reported registries), and patient-reported outcome measures. We also know whether there are any electrophysiology/biomarker data available for each registry (CMAP/DEXA/muscle imaging), although we do not collect those data as part of the core dataset.

Reference to document, if applicable:

For v1: https://treat-nmd.org/wp-content/uploads/2019/06/SMA-Full_Expanded_SMA_Core_Dataset.pdf

For v2: https://sma.treat-nmd.org/overview

38. Please specify in detail the information collected on the criterion "ventilation". Please address in particular the aspects of time of initiation and type of ventilation, local treatment options, and local decision criteria for ventilation.

We collect the following information, for both invasive and non-invasive ventilation:

- Ventilation status (e.g. previously, currently, never)
- Duration (e.g. part-time / full-time)
- We do not collect (in the core dataset) information on local treatment options or local decision criteria

Reference to document, if applicable:

For v1: See Section 10 (Pulmonary Function): https://treat-nmd.org/wp-content/uploads/2019/06/SMA-Full_Expanded_SMA_Core_Dataset.pdf

For v2: https://sma.treat-nmd.org/items/Pulmonary%20function

39. Which standardized procedures or measurement tools/scales do you use to document the course of disease in patients with clinically diagnosed SMA type 1 or with up to 3 copies of the *SMN2* gene?

☒ CHOP-INTEND score (Children´s Hospital of Philadelphia Infant Test of Neuromuscular Disorders)

☒ HFMS score (Hammersmith Functional Motor Scale)

☒ HFMS-E score (Hammersmith Functional Motor Scale - Expanded)

☒ HINE score (Hammersmith Infant Neurological Examination), Section 2

☒ Observed WHO score (World Health Organization Motor Development Milestones)

Do you use any other standardized procedures or measurement tools/scales to document the course of disease **in the target groups named above**?

Section 7 (Motor Function) is mandatory for every patient in every registry, regardless of data entry model, SMA type, or *SMN2* copy number. This section aims to capture a basic indication of motor function that is comparable across the entire cohort, regardless of issues such as access to physiotherapists, and is based on validated individual items from WHO and RULM.

In addition to this, clinician-reported registries must collect a minimum of one validated motor outcome measure per patient, per visit. Selection of the appropriate validated motor measure for any given patient is at the discretion of the registry and/or centre and/or treating physician. Scores and dates for any validated measure can be reported into the global registry.

It is feasible that in future, as the consensus on the most appropriate motor outcome measures grows, TREAT-NMD will look to select a small group of core motor scales which all registries will be required to collect, but in the current landscape this is not feasible. However, a recent report (July 2020) based on n10 of the n12 pilot registries and all n8 year 1 registries shows that there is already a natural emerging consensus across the registries, with the most commonly collected being CHOP-INTEND, HFMS, RULM, and 6MWT. I have asked the project funders for permission to share this full report with you.

Reference to document, if applicable:

For v1: See Section 7 (Motor Function) and Section 14 (Motor Measures): https://treat-nmd.org/wp-content/uploads/2019/06/SMA-Full_Expanded_SMA_Core_Dataset.pdf

For v2: https://sma.treat-nmd.org/items/Motor%20function and https://sma.treat-nmd.org/items/Motor%20measures

40. Which standardized measurement tools for determining health-related quality of life do you use as a third-party assessment (affected children) or a self-assessment (parents/other carers)?

Currently there is no quality of life assessment in the core dataset. Some registries collect this locally (various tools) but we do not collect it centrally.

For patient-reported outcome measures, as a mandatory minimum across all registries we collect:

- Patient Global Impression of Severity (PGI-S) at baseline
- Patient Global Impression of Improvement (PGI-I) at follow-up

In addition to this, all registries are encouraged to collect a validated patient-reported outcome measure for each patient.

Reference to document, if applicable:

For PGI-S and PGI-I: https://www.fda.gov/media/125041/download

41. Which data do you collect in the registry as potential "confounders" (e.g. duration of disease, indicators of disease severity, number of *SMN2* copies, comorbidity) in order to be able to address the impact of bias in analyses (e.g. of treatment comparisons)?

We collect all of the examples listed above, but I'm not sure what else would be classed as a confounder. The full datasets are available below for your reference.

Reference to document, if applicable:

For v1: https://treat-nmd.org/wp-content/uploads/2019/06/SMA-Full_Expanded_SMA_Core_Dataset.pdf

For v2: https://sma.treat-nmd.org/

42. Information for third parties (e.g. the G-BA) with regard to the reproducibility of the analysis:

☒ only aggregate results data are planned

☐ (anonymized) individual patient data sets are available under the following conditions (please briefly explain): we are looking ahead to potentially working with individual level data in the future but this is not currently offered.

Part 2: Quality

43. Is a detailed description available for your registry in terms of a "registry protocol"?

☒ no ☐ yes ☐ yes, see attachment

The individual registries that comprise the TREAT-NMD Global SMA Registry network will have their own registry protocols. The global registry is not a 'Study' as such so has not needed a core protocol before now. However, looking ahead to postmarketing and the development of our own Registry Platform for collecting and analysing data, we will be developing a core protocol upon which individual PMS study protocols can be based. The global registry Network is governed by the TREAT-NMD Global Data systems Oversight Committee (TGDOC) and all member registries agree to abide by our Charter and Standard Operating Procedure documents.

44. Are precise definitions and operationalizations available for the exposures, clinical events, outcomes and confounders for which you collect data in your registry?

☐ no ☒ yes

Reference to document, if applicable:

For v1: https://treat-nmd.org/wp-content/uploads/2019/06/SMA-Full_Expanded_SMA_Core_Dataset.pdf

For v2: https://sma.treat-nmd.org/

45. Is an up-to-date data set description and/or a coding manual available for your registry?

☐ no ☒ yes ☐ yes, see attachment

For v1: https://treat-nmd.org/wp-content/uploads/2019/12/uncategorized-2019.12.13_TREAT-NMD-SMA-Dataset-Manual-v1.pdf
For v2: https://sma.treat-nmd.org/

46. Do you conduct training on how to collect and record data for your registry?

☐ no ☒ yes
We provide an annual SMA dataset workshop for registry curators

47. Are there clearly defined inclusion and exclusion criteria for the registered patients?

☐ no ☒ yes

Genetic diagnosis of 5q SMA

48. Have you implemented measures in the registry to ensure the accuracy of the data and to provide information on error rates (e.g. through source data verification, internal and external audits, IT-based checks [e.g. cross-reference checks])?

☐ no ☐ yes ☒ partially

Reference to document, if applicable:

49. If you answered "yes" or "partially" to the previous question, could you briefly outline the main results of these checks?

This is complex for us as a federated hub/spoke model, as we have no direct control over the primary data collection activities. The way we work will also change dramatically over the coming years, to align with the emerging requirements of the SMA landscape. However, to try and summarise:

- We do not currently conduct any checks or audits at local registry level, although this may become necessary in the future.
- The v2 dataset specification includes validation rules for the registries to implement locally, and additional implementation notes where needed.
- We are currently building a dual-purpose registry platform:
    1. For member registries to use as their data collection tool if required
    2. To house a central data warehouse (CDW) for TREAT-NMD to collect/analyse data
- The data collection forms on the platform will comply with the core dataset and will have all the necessary validation rules built in. In addition to this, automated soft-checks will be based on expected values or ranges. Data checks and validation will happen on multiple levels:
    1. At the point of data entry (for registries using the platform)
    2. When the local curator submits to the CDW
    3. After the data is received in the CDW
- These rules and processes are still under development

Reference to document, if applicable:

50. Are changes in processes and definitions systematically documented in your registry ("documentation trail")?

☐ no ☒ yes ☐ partially

Changes to the dataset (including definitions) are systematically documented. Any changes to processes for global registry Enquiries are documented in updates to the TGDOC Charter or SOPs.

Reference to document, if applicable:

The latest version of the TGDOC Charter is in the final approval stages and will be uploaded to the TREAT-NMD website in the coming days.

51. How is the scientific independence of the registry ensured?

All member registries must have ethical approval to share data with the TREAT-NMD global registry, and industry is not permitted to be represented in TGDOC governance. All registries must sign a CDA and will soon also be asked to submit a Declaration of Interest form in case of any potential conflicts.

When an enquiry is received from any third party into the data in the global registry, it must first be approved by the TGDOC membership (by vote) to ensure it is an appropriate use of data, in line with the aims of the global registry, and in the best interests of the patients. The global registry does not receive any core funding, from industry nor any other source. It is self-financing using income generated from the registry enquiries mentioned above.

Reference to document, if applicable:

52. Is the funding of your registry secured in the medium term (4-6 years)?

☐ no ☐ yes ☒ unclear

Each member registry is funded in their own way. Coordination of the global registry Network is self-sufficient, any income made from Registry Enquiries is reinvested into the network and used for training and development needs.

53. Do you use exact dates for patients, diseases and events in the registry data sets?

☐ no ☒ yes ☒ partially (please briefly explain):

Registries are encouraged to collect full dates (where necessary) for local use, however TREAT-NMD will only ever collect partial dates (MM-YYYY) centrally.

Reference to document, if applicable:

54. Does the registry contain detailed information on drug therapy (active substance, dose, dose change, including dates)?

☐ no ☒ yes ☐ partially (please briefly explain):

Reference to document, if applicable:

For v1: See Section 11 (Therapies and Medications) https://treat-nmd.org/wp-content/uploads/2019/06/SMA-Full_Expanded_SMA_Core_Dataset.pdf

For v2: https://sma.treat-nmd.org/items/Therapies

55. Are adverse events in patients recorded systematically, including specific adverse events related to treatment with nusinersen and onasemnogene abeparvovec/dexamethasone?

☐ no ☐ yes ☒ partially (please briefly explain):

For each acute hospitalisation or comorbidity reported, we ask 'Was this also classed as an SAE in relation to a DMT for SMA?" If so, registries must record the DMT to which that SAE was related (onasemnogene abeparvovec, nusinersen, risdiplam)

Reference to document, if applicable:

For v1: See Section 12 (Hospitalisations and Comorbidities) https://treat-nmd.org/wp-content/uploads/2019/06/SMA-Full_Expanded_SMA_Core_Dataset.pdf

For v2: https://sma.treat-nmd.org/items/Hospitalisations

56. Are adverse events recorded using the standard terminology MedDRA?

☒ no ☒ yes - partially

In v1: Reason for acute hospitalisation is recorded using MedDRA and comorbidities are recorded using ICD-10 (and these are then linked to SAEs, see q21 above

In v2: Reason for acute hospitalisation and comorbidities can both be recorded using either MedDRA, ICD-10 or ICD-11

57. Do you collect data on the comorbidities of registered patients?

☐ no ☐ yes ☒ yes, with ICD 10 codes

58. In the current structure of your registry, how quickly can the required analyses of data or anonymized individual patient data sets be made available for analysis by third parties?

Within ___ months

We cannot currently provide individual patient data sets. We can conduct internal analysis on aggregate data and provide a report for third parties. The length of time taken will depend on the complexity of the data requirements but can usually be completed within 12 weeks of contract execution.

59. Does your registry have the technical and organizational flexibility to implement data set expansions (e.g. additional data collection dates and/or additional measurement tools for specific analysis purposes) within a shorter period of time?

☐ no ☐ yes ☐ yes, under certain conditions (please briefly explain):

For permanent expansions to the core dataset: we have a formal revision plan in place to review and implement requests; including at short notice if urgent.

For one-off data enquiries: Additional data items may be included in a specific data enquiry into the global registry Network for SMA, however we cannot guarantee the number of registries that collect any non-core dataset items.

For post-marketing studies: This could be discussed, if there was a requirement for some additional data capture by a sub-set of registries for the duration of a particular study. However, we cannot of course speak for the individual registries themselves in terms of feasibility of a given item.

If yes, within ___ months

60. How do you rate the completeness of the data on children with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene in terms of losses to follow-up or dropouts?

☐ very good ☐ good ☐ average ☐ sufficient ☐ poor ☐ very poor

Please briefly explain:

Not possible for TREAT-NMD to answer. We do not monitor dropouts or LTFU centrally as we currently only collect aggregate data.

61. How do you rate the completeness of the individual data sets generated at each data collection time for children with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene?

☐ very good ☐ good ☐ average ☐ sufficient ☐ poor ☐ very poor

Please briefly explain:

Not possible for TREAT-NMD to answer. This will vary significantly from registry to registry. As a federated hub/spoke model we have no direct control over the primary data collection processes, nor access to the data.

62. How do you rate the accuracy of the data collected for the subgroup of children with SMA described above?

☐ very good ☐ good ☐ average ☐ sufficient ☐ poor ☐ very poor

Please briefly explain your opinion:

Not possible for TREAT-NMD to answer. This will vary significantly from registry to registry. As a federated hub/spoke model we have no direct control over the primary data collection processes, nor access to the data. We currently only collect aggregate data. When the new registry platform is in place (due for completion summer 2021) we will be able to judge this much better.

63. How do you rate the consistency over time of the data collected in your registry for children with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene?

☐ very good ☐ good ☐ average ☐ sufficient ☐ poor ☐ very poor

Please briefly explain your opinion:

Not possible for TREAT-NMD to answer. Only aggregate data collected centrally.

64. From a quality point of view, are there filter options for the data sets in your registry, e.g. according to participating centres or the type of persons entering data (doctors, patients/parents)?

☐ no ☒ yes

Part 3: Registered patients

65. Does your registry include patients from Germany with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene and if so, how many?

☐ no ☐ yes _____ (number of patients), included since the year _____

66. In your opinion, are the data in your registry representative of children from Germany with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene?

☐ no ☐ yes ☐ unclear

Please briefly explain:

67. Does your registry include patients from Germany with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene who have not received treatment with nusinersen or onasemnogene abeparvovec?

☐ no ☐ yes _____ (number of patients)

If you answered "yes", are the data collected from untreated children consistent with those of treated children

☐ no ☐ yes

68. Have you implemented an effective procedure to avoid double or multiple registrations of patients in your registry?

☐ no ☐ yes (please briefly explain):

Reference to document, if applicable:

Part 4: Registry-specific questions

TREAT-NMD:

- What is the status of the ongoing revision of the data set ("mandatory" and "highly encouraged" items)? What are the main changes/extensions proposed?
  V2 draft is available here. Open for feedback until 11 Sept and will be confirmed at the end of September. Registries already collecting v1 will be asked to implement applicable changes within 6 months. https://sma.treat-nmd.org/

- How many treatment centres in Germany collect the extended data sets and are they also regularly pooled at the international level by TREAT-NMD, or does this only apply to the core data set?
  We only collect/pool the core dataset.
  - Patient-reported registry at Munich: fully compliant and intending to submit data for TREAT-NMD enquiries.
  - SMArtCARE registry at Freiburg: The SMArtCARE v1 dataset and the TREAT-NMD v1 dataset were very well aligned in 2018, however I have been unable to obtain the current SMArtCARE dataset to do a similar alignment for v2. We cannot currently say whether they plan to submit data as part of the TREAT-NMD global registry
- How many new data sets from German treatment centres for patients with clinically diagnosed type 1 SMA or with up to 3 copies of the *SMN2* gene are included in TREAT-NMD each year?
  - Unknown – see above.
- What is the status of the planned collaboration with RESTORE? Initial discussions on data sharing did not progress as the request was for individual level data. Nevertheless, we have been working closely to harmonise our datasets and a detailed gap analysis has been carried out. I have asked permission to share this with you.

Appendix C Fulfilment of nationally and internationally used quality criteria by the identified registries

On the basis of the available information, the following table shows the extent to which the two identified registries RESTORE and SMArtCARE fulfil nationally and internationally used quality criteria. The list of quality criteria is taken from rapid report A19-43 (Table 7 from A19-43 excluding criteria 35 to 45, which refer to specific registry studies).

For the meta-registry TREAT-NMD SMA global registry, a presentation of the quality criteria was omitted because, according to the feedback provided by the registry operators of the meta-registry in Appendix B.3, this depends on the individual quality of each national registry and therefore a heterogeneous quality of the national registries can be assumed. A presentation of the quality criteria realated to the meta-registry is therefore not meaningful.

No.	Quality criterion	RESTORE	SMArtCARE
	Systematics		
1	Detailed registry description (protocol)	unclear	yes
	Standardization		
2	Precise definition / operationalization of exposures, clinical events, outcomes and confounders	unclear	yes
3	Current data plan / coding manual	unclear	yes
4	Use of standard classifications (e.g. ICD-10) and terminology (e.g. MedDRA)	unclear	yes
5	Use of validated standard data collection tools (questionnaire, scales, tests)	yes (for *de novo* centres)	yes, but no collection of data on health-related quality of life
6	Training courses on data collection and recording	no	yes
7	Implementation of a consensual disease-specific core data set	yes (for *de novo* centres)	yes
8	Use of exact dates for the patient (e.g. birth, death, pregnancy)	unclear	yes
9	Use of exact dates of disease (e.g. definitive diagnosis, clinically relevant events)	yes (for diagnosis), otherwise unclear	yes
10	Use of exact dates for important examinations	unclear	yes

No.	Quality criterion	RESTORE	SMArtCARE
11	Use of exact dates for treatments / interventions (e.g. for drugs: start / stop date, dose, dose changes)	yes	yes, with limitations (no dose query for nusinersen)
	Achievement of the recruitment goal / sample composition		
12	Clearly defined inclusion and exclusion criteria for registry patients	yes	yes
13	Completeness of registry patients (complete recording or representative sample)	unclear	unclear
14	Strategies to avoid selection bias in patient inclusion to achieve representativeness	in part (for *de novo* centres): consecutive inclusion planned, but completeness only for onasemnogene named as goal	yes (consecutive inclusion)
	Validity of data collection		
15	Completeness of data per time point of data collection	not ensured	aimed for by requirements
16	Completeness of data collection time points (loss-to-follow-up, drop-outs)	not ensured	aimed for by requirements
17	Accuracy of data	unclear	with limitations, as there is no source data verification
18	Data consistency over time	unclear	yes
19	Source data verification (e.g. for 10% randomly selected patients per study centre)	unclear	no
20	Registry monitoring by internal audits	unclear	no
21	Registry monitoring by external audits	unclear	no
22	QM system (if necessary, with regular collection of quality indicators)	unclear	yes
23	SOPs for data collection	unclear	yes
	Superordinate quality criteria		
24	Registry transparency (e.g. funding, decision paths, conflicts of interest)	no	yes
25	Scientific independence	not ensured	yes
26	Secure funding (for planned data collection period)	to be assumed	yes
27	Steering committee, executive committee	yes	yes

No.	Quality criterion	RESTORE	SMArtCARE
28	Currency of the registry documents (e.g. protocol, data plan, statistical analysis plan, declaration of consent etc.)	unclear	yes
29	Respect of patient rights and data protection, consideration of ethical aspects	yes	yes
30	Timeliness (currentness and rapid availability of the required results)	unclear	yes
31	Flexibility and adaptability (e.g. for embedding studies, for further data collection, in the event of changes in the health care situation)	yes	yes
32	Documentation trail - documentation of all process and definition changes in the registry	unclear	yes
33	Audit trail - documentation and attributability of all data transactions	unclear	yes
34	Linkability with other data sources	aimed for	aimed for
	Other possible criteria from a regulatory perspective		
46	Recording and handling of adverse events according to regulatory requirements	unclear, to be assumed for onasemnogene abeparvovec	yes

Appendix D Studies on nusinersen

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT04488133 [32]	Open, 1-arm	Children (3–36 months) with 5q SMA (homozygous gene deletion, mutation or mixed heterozygosity), ▪ who have previously received onasemnogene abeparvovec ▪ who have not yet received nusinersen	Planned: N = 60	Screening: NR Treatment: 659 days Follow-up: up to day 778	Not yet recruiting (27.07.2020) NR	Not relevant, onasemnogene pretreatment
NCT03878030 [33]	Prospective observational study	Adults (18–60 years) with 5q SMA type II or III	N = 12	Screening: NR Treatment: SOC + repeated intrathecal nusinersen Follow-up: 2 years	Active, not recruiting (28.02.2020) USA 04/2019–ongoing	Not relevant, adults
NCT04050852 [34]	Open, 1-arm	Patients (5–21 years) with SMA of any type who have already consented to or started treatment with nusinersen	Planned: N = 5-10	Screening: NR Treatment: repeated nusinersen Follow-up: 12 months	Recruiting (07.08.2020) USA 07/2019–ongoing	Not relevant, no relevant outcomes (lung function, potential AEs irrelevant for number of patients and follow-up time)

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT04419233 [35] (PANDA)	Prospective observational study	Patients with 5q SMA from China who are newly prescribed nusinersen according to local regulatory approval but have not yet started treatment	Planned: N = 50	Screening: NR Treatment: repeated nusinersen Follow-up: 2 years	Recruiting (18.08.2020) China 08/2020–ongoing	Not relevant, routine data from China
NCT04317794 [36]	Prospective observational study	Patients with 5q SMA from Korea who are already using or have been newly prescribed nusinersen according to local regulatory approval	Planned: N = 145	Screening: NR Treatment: nusinersen for 2 years Follow-up: 2 years	Recruiting (11.06.2020) multicentre Korea 07/2019–ongoing	Not relevant, routine data from Korea
NCT02052791 [37] (396443-CS12)	Open, 1-arm	Patients with clinical symptoms of SMA who received nusinersen in the 396443-CS2 and 396443-CS10 studies and completed the studies	N = 47	Screening: NR Treatment: repeated intrathecal nusinersen Follow-up: up to 24 months	Multicentre USA 01/2014–01/2017	Not relevant, follow-up from dose-finding

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT02386553 [38] (NURTURE) also in EudraCT: 2014-002098-12	Open, 1-arm	Children ≤ 6 weeks with presymptomatic 5q SMA (homozygous gene deletion, mutation, or mixed heterozygosity) with 2 or 3 copies of the *SMN2* gene	N = 25	Screening: NR Treatment: repeated intrathecal nusinersen Follow-up: up to age of 8 years	Active, not recruiting (03.12.2019) multicentre Global 05/2015–ongoing	Potentially relevant
NCT01703988 [39,results: 40] (396443-CS2) also in EudraCT: 2017-000327-27	Open, parallel, not randomized	Children (2–15 years) with symptomatic 5q SMA (homozygous gene deletion or mutation) or mutation) without respiratory failure or gastric tube	Nusinersen 3 mg: N = 8 Nusinersen 6 mg: N = 8 Nusinersen 9 mg: N = 9 Nusinersen 12 mg: N = 9	Screening: NR Treatment: 85 days Follow-up: up to end of study (85 days)	Multicentre USA 10/2012–01/2015	Not relevant, dose finding
NCT01780246 [41] (396443-CS10)	Open, 1-arm	Children (2–15 years) with clinical symptoms of SMA who received nusinersen in the ISIS 396443-CS1 study	N = 18	Screening: NR Treatment: intrathecal nusinersen Follow-up: up to 24 weeks	Multicentre USA 01/2013–02/2014	Not relevant, follow-up dose finding

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT01839656 [42,results: 43] (396443-CS3A) also in EudraCT: 2017-000621-12	Open, parallel, not randomized	Children (< 210 days) with 5q SMA (homozygous gene deletion or mutation) whose SMA symptoms started at an age of ≥ 21 days and < 6 months	Nusinersen 6 mg: N = 4 Nusinersen 12 mg: N = 16	Screening: NR Treatment: intrathecal nusinersen up to Day 1261 Follow-up: 1352 days for milestones in motor development, maximum up to end of study	Multicentre in Canada and USA 05/2013–08/2017	Potentially relevant (12 mg arm)
NCT02292537 [44,results: 45] (CHERISH, 396443-CS4)	RCT, parallel, blinded	Children (2–12 years) with diagnosed SMA ▪ whose symptoms occurred at > 6 months ▪ who can sit independently but have never been able to walk independently ▪ HFMSE of ≥ 10 and ≤ 54 at screening ▪ without respiratory failure or feeding tube	Nusinersen (N = 84) Sham injection (N = 42)	Screening: NR Treatment: intrathecal injections at Day 1, 29, 85, 274 Follow-up: up to 15 months	Multicentre global 11/2014–02/2017	Potentially relevant

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT02865109 [46]	Expanded Access Program	Patients with 5q SMA (homozygous gene deletion, mutation, or mixed heterozygosity) type I (onset of symptoms at an age ≤ 6 months) who are unable to participate in an ongoing clinical program and have never received nusinersen	NR	Screening: NR Treatment: repeated nusinersen	Multicentre global 2016–ongoing	Not relevant, no recording of outcomes

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT04089566 [47] (DEVOTE) also in EudraCT: 2019-002663-10	RCT, sequential, blinded	Patients with 5q SMA (homozygous gene deletion or mutation or mixed heterozygosity). ▪ Part A: ▫ age 2–15 years ▫ start of clinical symptoms at age > 6 months (later-onset SMA) ▫ without respiratory failure or feeding tube ▪ Part B: ▫ start of symptoms at age ≤ 6 months (infantile-onset): age ≤ 7 months ▫ start of symptoms at age > 6 months (later-onset): age 2–< 10 years, children must be able to sit independently, but were not allowed to have walked independently; HFMSE ≥ 10 and ≤ 54 at screening ▫ without respiratory failure or feeding tube ▪ Part C: adults able to walk ≥ 18 years, who received nusinersen at screening with the first nusinersen dose ≥ 1 year before screening	Planned: N = 125	Screening: NR Treatment: In all study arms: nusinersen or sham injection in different doses/schemes intrathecal up to maximum Day 279 Follow-up: up to Day 302	Recruiting (09.07.2020) multicentre global 03/2020–ongoing	Potentially relevant (arm with approved dose)

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT02594124 [48] (SHINE) also in EudraCT: 2015-001870-16	Not randomized, blinded, parallel	Patients with SMA who have participated in studies on nusinersen	Currently N = 292 Arm 1: patients from the ISIS 396443-CS3B study Arm 2: patients from the ISIS 396443-CS4 study Arm 3: patients from the ISIS 396443-CS12 study Arm 4: patients from the ISIS 396443-CS3A study Arm 5: patients from the 232SM202 study	Screening: NR Treatment: repeated intrathecal nusinersen Follow-up: up to Day 1814	Active, not recruiting (14.04.2020) multicentre global 11/2015–ongoing	Potentially relevant follow-up of clinical studies
NCT02462759 [49,results: 50] (EMBRACE, 232SM202) also in EudraCT: 2014-003657-33	RCT, parallel, blinded	Children with 5q SMA (homozygous gene deletion or mutation or mixed heterozygosity) without SMA symptoms at birth or within the first week of life and without permanent respiratory support[a] ▪ start of symptoms at the age of ≤ 6 months with 3 *SMN2* copies or ▪ start of symptoms at the age of ≤ 6 months with an age at screening of > 7 months with 2 *SMN2* copies or ▪ start of symptoms at the age of > 6 months with an age at screening of ≤ 18 months with 2 or 3 *SMN2* copies	N = 21 Arm 1: nusinersen (N = 14) Arm 2: sham injection followed by nusinersen (N = 7)	Screening: NR Treatment: nusinersen or sham injection Follow-up: up to Day 1138	Discontinued early to transfer patients into extension study NCT02594124 (27.01.2020) 08/2015–discontinued early	Potentially relevant

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT02193074 [51,results: 52] (ENDEAR, 396443-CS3B)	RCT, parallel, blinded	Children (≤ 210 days) with SMA and 2 *SMN2* copies	Nusinersen (N = 80) Sham injection (N = 41)	Screening: NR Treatment: nusinersen or sham injections intrathecal up to Day 302 Follow-up: up to 13 months	Discontinued early multicentre global 08/2014–11/2016	Potentially relevant
NCT03709784 [53] (SAS)	Observational study	Adults able or not able to walk (18–70 years) with 5q SMA (homozygous gene deletion or mutation or mixed heterozygosity) type II or III who plan to receive treatment with nusinersen as part of their clinical regimen	Planned: N = 73	Screening: NR Treatment: repeated intrathecal nusinersen Follow-up: up to 30 months	Recruiting (11.08.2020) multicentre Canada and USA 08/2018–ongoing	Not relevant, adults
NCT01494701 [54] (396443-CS1)	Not randomized, parallel, open	Symptomatic children (2–14 years) with SMA (homozygous *SMN1* deletion) without respiratory failure or feeding tube	Cohort 1 (N = 6) Cohort 2 (N = 6) Cohort 3 (N = 6) Cohort 4 (N = 10)	Screening: NR Treatment: intrathecal nusinersen Follow-up: up to 88 days	Multicentre USA 11/2011–01/2013	Not relevant, dose finding

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT04404764 [55]	Retrospective observational study (patient-registry)	Patients (≥ 6 months) with 5q SMA type II or III, who are already being treated with nusinersen or are eligible for treatment with nusinersen, Symptom onset > 6 months and < 19 years for type II or > 18 months and < 19 years for type III, without invasive ventilation	Planned: N = 100	Screening: NR Treatment: repeated intrathecal nusinersen Follow-up: up to 6 months	Recruiting (01.06.2020) multicentre Brazil 05/2020–ongoing	Not relevant, Brazilian cohort
NCT04159987 [56]	Open, 1-arm	Adults (≥ 18 years) with 5q SMA (homozygous gene deletion or mutation or mixed heterozygosity) type II (symptom onset at age > 6 months, ability to sit freely but never walked) who are wheelchair-bound	Planned: N = 20	Screening: NR Treatment: intrathecal nusinersen Follow-up: up to 27 months	Not yet recruiting (12.11.2019) multicentre 11/2019–ongoing	Not relevant, adults
NCT04139343 [57]	Observational study (case-control study)	Adults (17-70 years) with SMA (homozygous gene deletion) type II (ability to sit with support) or III (ability to stand and walk freely), without respiratory failure	Planned: N = 140 Cohort 1: SMA control Cohort 2: nusinersen Cohort 3: (healthy) control patients only for baseline visit	Screening: NR Treatment: repeated nusinersen Follow-up: up to 15 years	Recruiting (28.10.2019) The Ohio University Medical Center, USA 08/2018–ongoing	Not relevant, adults

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
NCT03032172 (Jewelfish) [58] also in EudraCT: 2016-004184-39	1-arm, open	Patients (6 months–60 years) with 5q SMA previously enrolled in the BP29420 (Moonfish) study or treated with any of the following agents: nusinersen, olesoxime, AVXS-101	Currently: N = 174	Screening: NR Treatment: risdisplam Follow-up: 2 years	Active, not recruiting (21.07.2020) multicentre global 03/2017–ongoing	Not relevant, non-relevant intervention
NCT03339830 [59]	Patient registry IO-SMA, prospective	Patients of any age with genetically confirmed SMA (diagnosed at age < 18 months) type I (have never been able to sit freely), type II or III (treated with an approved treatment for SMA or with a treatment from an Expanded Access Program)	Planned: N = 100	Screening: NR Treatment: approved treatment for SMA or treatment from an Expanded Access Program Follow-up: up to 5 years	Recruiting multicentre France 10/2017–ongoing	Not relevant, French registry, consideration in case of suitability via data collection in disease registries
NCT04177134 [60]	French SMA patient registry, retro- and prospective	Patients with 5q SMA type I, II, III, or IV who are followed up or diagnosed between 01.09.2016 and 31.08.2024, are treated in French reference centres, and have health insurance coverage	Planned: N = 1000	Screening: NR Treatment: NR Follow-up: up to 9 years	Recruiting (05.02.2020) France 01/2020–ongoing	Not relevant, French registry, consideration in case of suitability via data collection in disease registries

Table 11: Characteristics of studies on nusinersen (source: ClinicalTrials.gov, keyword "nusinersen", date of access 16 September 2020, comparison with EU CTR, keyword "nusinersen", date of access 23 September 2020) (multi-page table)

Study	Study design	Population	Interventions (number of included / randomised patients)	Study duration	Recruitment status, if ongoing Location and period of study conduct	Relevance for RPDC-GSAV
a. Ventilation ≥ 16 hours/day for more than 21 days at screening, permanent tracheostomy CHOP-INTENT: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE: Hammersmith Functional Motor Scale Expanded; HINE: Hammersmith Infant Neurological Examination; MFM: Motor Function Measure; N: number of included/randomized patients; NR: not reported; RCT: Randomized controlled trial; RPDC-GSAV: routine practice data collection according to the "Gesetz für mehr Sicherheit in der Arzneimittelversorgung" (Law for More Safety in the Supply of Medicines); SMA: spinal muscular atrophy; SMN: survival motor neuron; SOC: standard of care; WHO: World Health Organization						