Study protocol

Study title:	Registry study to record the provision of assistive devices, remedies, medications, and nursing care in an inter-cohort comparison of patients with ALS and other neurological diseases.
Sponsor:	Ambulanzpartner Soziotechnologie APST GmbH Friedrichstraße 90 10117 Berlin
Principal	Investigator: Prof. Dr. Thomas Meyer Ambulanzpartner Soziotechnologie APST GmbH Friedrichstraße 90 10117 Berlin Germany
Date:	22.12.2020 Version 3.1

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1. List of abbreviations

5q-SMA	SMA patients with a genetic disposition on chromosome 5q
ALS	Amyotrophic lateral sclerosis.
ALSFRS-EX	Amyotrophic Lateral Sclerosis Functional Rating Scale - extended
ALSFRS-r	Amyotrophic Lateral Sclerosis Functional Rating Scale - revised
APST	Ambulanzpartner Soziotechnologie APST GmbH
APVP	Ambulanzpartner supply platform
BDSG	German Federal Data Protection Act
BMI	Body-Mass-Index
CEO	Chief Executive Officer (Managing Director)
DSGVO	Data Protection Basic Regulation
FAC	Functional Ambulation Categories
ID	Identification
MIE	Mechanical Insufflator/Exsufflator
NPS	Net Promotor Score
NRS	Numeric Rating Scale
PEG	Percutaneous endoscopic gastrostomy
SMA	Spinal muscular atrophy
TSQM-9	Treatment Satisfaction Questionnaire for Medication

2. List of Figures

3. Declaration of gender neutrality

For reasons of better readability, the simultaneous use of masculine and feminine forms of speech has been dispensed with. All references to persons nevertheless apply to all persons.

4. Study contact - Information about the study management

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5. Introduction

5.1. Background and rationale

The aim of the registry study is to collect data on the provision of assistive devices, therapies (physiotherapy, occupational therapy, speech and language therapy), medication and care services for patients with chronic neurological diseases. The data collected should describe the reality of care with assistive devices, remedies, medications, and nursing services for patients with chronic neurological diseases and serve to generate hypotheses for future studies.

5.2. About APST

APST is a spin-off of Charité - Universitätsmedizin Berlin in 2010. APST has developed the digital platform "Ambulanzpartner Versorgungsportal (APVP)" for the purpose of care management and care research. The APVP is used to support complex care processes and to record the treatment reality in the provision of assistive devices, therapies, medicines, and care services. The thematic focus of the APST is on chronic neurological diseases, especially ALS, SMA and other motor neuron diseases.

5.3. Objective

In the treatment of people with chronic neurological diseases, numerous assistive devices, medications, and forms of therapy are used. Especially in the case of rare and severe neurological diseases, there are open research questions about the optimal timing and necessary extent of neurological treatment. Furthermore, there are only a few studies available on how the treatment results are evaluated by the patients themselves. The systematic recording of neurological treatment and its evaluation by patients should help to improve the care of patients with chronic neurological diseases. The results of the registry study will be published in scientific publications and used for the development of neurological treatment guidelines (Fürstenau et al. 2021, Fürstenau et al. 2020, Meyer er al. 2021, Meyer et al. 2020, Spittel et al. 2021, Meyer et al. 2019, Funke et al. 2018, Meyer et al. 2018, Funke et al. 2015). The study results will continue to be used to promote the development of innovative assistive devices and assistive technologies as well as medications or to optimize existing care concepts.

The registry study is structured in modules. Digit-Care forms the basic module, which maps the provision of assistive devices, therapies, medications, and care for patients with chronic neurological diseases. Based on Digit-Care, patients can participate in other specific modules depending on the indication, questions, and consent.

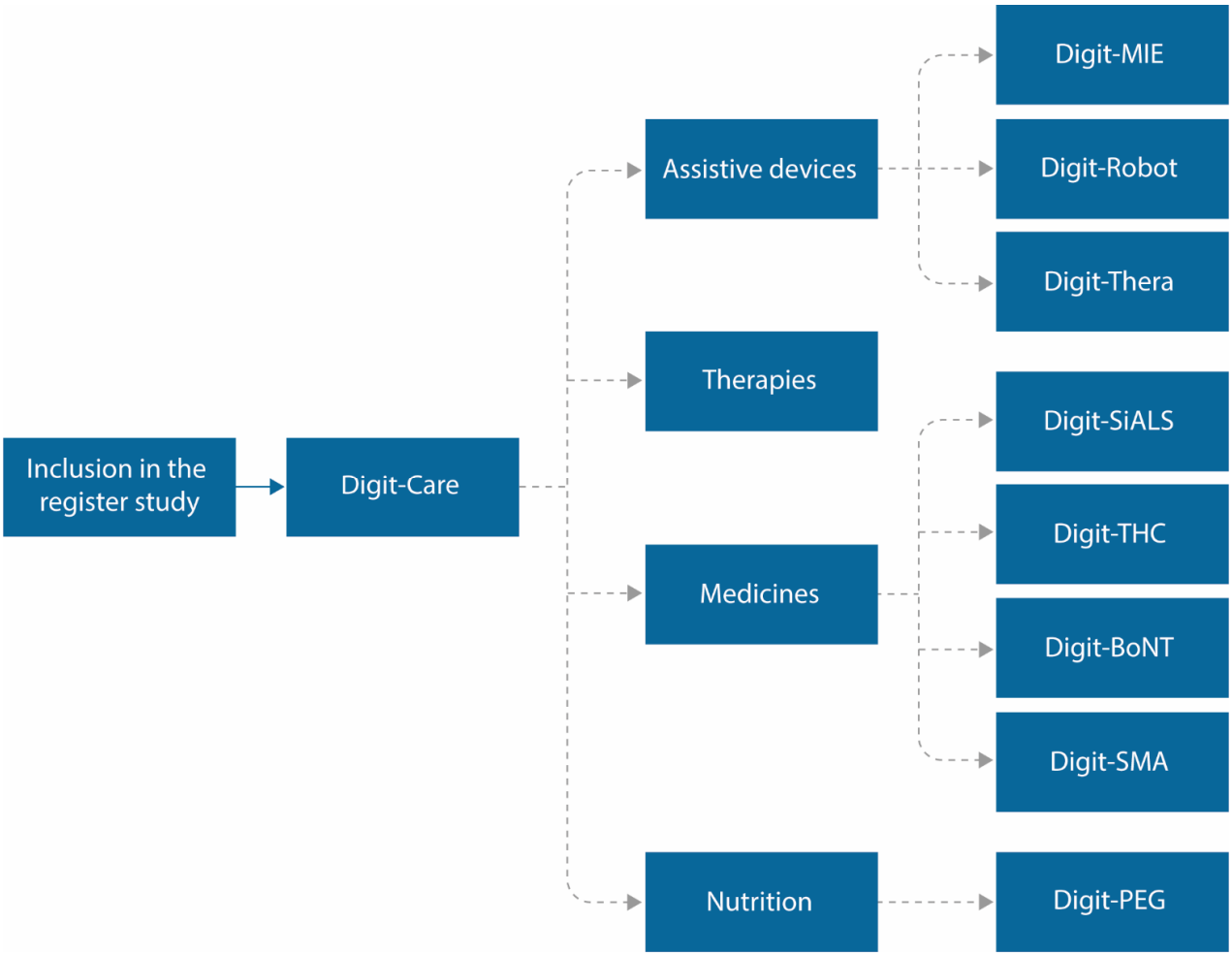

Figure 1: Modules of the registry study. *Digit-Care forms the basic module of the registry study. Other modules are additionally used depending on the indication, question, and consent of the patients. Therapies include physiotherapy, occupational therapy, speech and language therapy.*

The modules of the registry study examine different cohorts, which are characterized as follows:

- **Digit-Care:** Investigation of the supply of assistive devices, therapies, medicines, nutrition, and care in patients with chronic neurological diseases.
- **Digit BoNT**: To investigate the use behavior and user experience in patients with spasticity or dystonia who have received botulinum toxin type A treatment.
- **Digit SiALS**: Investigation of application behavior and user experience in patients with ALS and sialorrhea who received treatment with botulinum toxin type A.

- **Digit-MIE:** Investigation of the application behavior and user experience in patients with ALS who received a supply of a Mechanical Insufflator-Exsufflator (MIE).
- **Digit-PEG:** To investigate the supply of medications and nutritional products in patients with ALS and dysphagia who have received treatment with a Percutaneous Endoscopic Gastrostomy (PEG).
- **Digit-SMA:** Investigation of clinical characteristics as well as treatment expectancy and therapy experience in patients with 5q-associated SMA.
- **Digit-Robot:** Investigation of clinical characteristics, expectation, application behavior and user experience in patients who received a fitting with a robotic arm.
- **Digit-Thera:** Investigation of the application behavior and user experience in patients with ALS who received a supply of a therapeutic motor exercise device.
- **Digit-THC**: Investigation of use behavior and user experience in patients with ALS receiving tetrahydrocannabinol:cannabidiol (THC:CBD) treatment.

6. Data Analysis Plan

6.1. Study design

The registry study is a non-interventional analytical observational study for inter-cohort comparison. The study will be conducted multicenter at neurological outpatient clinics, university outpatient clinics, outpatient clinics for patients with disabilities or in specialized practices of SHI-accredited physicians. This register study will be realized and evaluated according to the STROBE criteria for observational studies.

6.2. Subjects

The registry study will enroll up to 25,000 patients, whose data will be examined prospectively and retrospectively. The cohort includes patients with chronic neurological diseases who have received care with assistive devices, therapies, medicines or nursing care.

6.3. Time frame

The total duration of the registry study covers the period from 03/15/2011 to 12/31/2024. Data from the period from 03/15/2011 to 10/28/2015 were collected based on patient informed consent retrospectively and included in the study for evaluation. Since October 29, 2015, data have been collected prospectively.

The cohorts in the different modules of the registry study will be examined in a temporally differentiated manner. The following modules will be conducted:

- Digit-Care: since March 2011
- Digit-BoNT: since May 2017
- Digit-MIE: since July 2018
- Digit-SMA: since July 2019
- Digit-Robot: since March 2019
- Digit-Thera: since February 2019
- Digit-PEG: since January 2021
- Digit-SiALS: since March 2021
- Digit-THC: since May 2017

7. Patient cohort

7.1. Informed consent and study information

Patients are fully educated and informed about the study prior to inclusion in the registry study. For this purpose, patients receive an informed consent form and a study information explaining the purpose of the study, the study procedure, the risks, the study discontinuation criteria, advantages of study participation, data protection and data processing.

7.2. General inclusion and exclusion criteria for the registry study.

Inclusion and exclusion criteria were defined for participation in the registry study and applied across all cohorts. These are outlined below:

7.2.1. Inclusion criteria:

- Patients from the age of 18
- Diagnosis of a chronic neurological disease

7.2.2. Exclusion Criteria:

- Lack of willingness to cooperate
- unwillingness to store and share medical data collected in the registry study.

7.3. Other criteria

Fulfillment of the inclusion and exclusion criteria (see section 7.2) allows participation in the register study (basic module "Digit-Care"). For participation in specific modules beyond the basic module "Digit-Care", additional inclusion criteria have been defined, which are presented below:

- **Digit-BoNT**: Diagnosis of spasticity or dystonia and treatment with botulinum toxin type A.
- **Digit-MIE**: Diagnosis of ALS or other neuromuscular disease and provision of a MIE.
- **Digit SMA**: Diagnosis of 5q-associated SMA and disease-modifying therapy.
- **Digit-Robot**: Diagnosis of ALS, SMA or other motor neuron disease and fitting with a robotic arm.
- **Digit-Thera**: Diagnosis of ALS as well as supply with a therapeutic motor exercise device.
- **Digit-PEG**: Diagnosis of ALS and treatment of PEG
- **Digit-SiALS:** Diagnosis of ALS and treatment of sialorrhea with botulinum toxin type A.
- **Digit-THC**: Diagnosis of ALS as well as treatment with THC:CBD.

8. Data acquisition

8.1. Data categories

In the modules of the registry study, different categories of treatment- and care-related data are collected, evaluated, and analyzed:

- Diagnoses and classifications of diseases
- Clinical features and symptoms, partly using scales

- Measurement parameters, biomarker findings and genetic findings of chronic neurological diseases
- Supply of assistive devices, therapies, medicines, or nursing care
- Medical and socio-medical circumstances of the supply with assistive devices, therapies, medicines, or nursing care
- Expectation of treatment prior to the provision of assistive devices, therapies, medicines, or nursing care
- Application behavior in the supply of assistive devices, therapies, medicines, or nursing care
- Evaluation and user experience of assistive devices, therapies, medicines, or nursing care

8.2. Modalities of data collection

The data mentioned in section 8.1 are collected in the following modalities:

- Data collected through the Ambulanzpartner platform (APVP).
- Data collection forms completed by a physician or study coordinator.
- Data collection sheets completed by the patient.
- Telephone interviews conducted by a physician or study coordinator.
- Online surveys conducted by the patient via an internet application for APVP.

8.3. Variables

8.3.1. Digit-Care (basic module)

- Demographic data
- Diagnoses and classifications of diseases
- Clinical features and symptoms, partly using scales
- Measurement parameters, biomarker findings and genotype
- Data on the supply of assistive devices
- Data on the provision of therapies
- Data on the provision of nutrition
- Data on provsion of medicines
- Evaluation and user experience of assistive devices, therapies, medicines, or nursing care

8.3.2. Digit-BoNT

- Data on provsion of medicines
- Net Promotor Score (NPS) (Hamilton et al. 2014)
- Treatment Satisfaction Questionnaire for Medication (TSQM-9) (Atkinson et al. 2004).

8.3.3. Digit-MIE

- Data on supply and provision of MIE
- ALS Functional Rating Scale revised (ALSFRS-r) (Cedarbaum et al. 1999).
- Numeric Rating Scale (NRS) (Serlin et al. 1995).
- Application behavior and user experience data.

8.3.4. Digit-PEG

- Data on provision on nutrition
- Data on provsion of medicines
- Application behavior and user experience data
- ALS Functional Scale (ALSFRS-r) (Cedarbaum et al. 1999).

8.3.5. Digit-SMA

- Drug supply data
- Data on provsion of medicines
- ALS Functional Rating Scale extended (ALSFRS-EX) (Abdulla et al. 2013).
- SMA Functional Rating Scale (SMA-FRS) (Elsheikh et al. 2009).
- Functional Ambulation Categories (FAC) (Mehrholz et al. 2007).
- Treatment Satisfaction Questionnaire for Medication (TSQM-9) (Atkinson et al. 2004).
- Net Promotor Score (NPS) (Hamilton et al. 2014)

8.3.6. Digit-Robot

- Data on the provision of assistive devices with robotic assistance systems
- Application behavior and user experience data
- ALS Functional Rating Scale extended (ALSFRS-Ex) (Abdulla et al. 2013).
- Net Promotor Score (NPS) (Hamilton et al. 2014)

8.3.7. Digit-Thera

- Data on the supply of assistive devices with therapeutic motor exercise devices
- Application behavior and user experience data
- ALS Functional Rating Scale revised (ALSFRS-r) (Cedarbaum et al. 1999).
- Net Promotor Score (NPS) (Hamilton et al. 2014)

8.3.8. Digit-SiALS

- Data on provsion of medicines
- ALS Functional Rating Scale revised (ALSFRS-r) (Cedarbaum et al. 1999).
- Net Promotor Score (NPS) (Hamilton et al. 2014)

8.3.9. Digit-THC

- Data on provsion of medicines
- ALS Functional Rating Scale revised (ALSFRS-r) (Cedarbaum et al. 1999).
- Net Promotor Score (NPS) (Hamilton et al. 2014)
- Treatment Satisfaction Questionnaire for Medication (TSQM-9) (Atkinson et al. 2004).

9. Statistical methods

Descriptive statistics and significance analyses are performed for the aggregation and interpretation of data. Descriptive analyses (frequency distributions in percent, mean values, medians, modal values, standard deviations) are used to compare frequencies within the parameters under investigation. Significance analyses describe the demonstrated difference between individual groups. Depending on the template of the data (metric, nominal scale, ordinal scale), different statistical tests are used:

- The t-test is used for significance analysis of metric data. In addition, confidence intervals are calculated and examined for differences between different groups. Statistical effect sizes of mean differences are calculated using Cohen's (1988) effect size d and classified as follows: small effect size: $d \geq 0.2$, medium effect size: $d \geq 0.5$, and large effect size: $d \geq 0.8$ (Cohens, 1988).
- Significant differences between parameters or subgroups of nominal scaled data are assessed by cross-tabulations, the chi-square test, or Fisher's exact test.
- For statistical significance analysis of ordinal scaled data, the Mann-Whitney-U test, the Kruskal-Wallis test or the Wilcoxon test is used. Depending on the question, the normal distribution of the data is checked by means of the Shapiro-Wilk test before statistical testing.

Correlations of clinical outcomes (e.g., treatment expectancy, treatment satisfaction, etc.) are calculated using linear regression models including potential cofactors. Results of longitudinal observations are also analyzed considering cofactors. Statistical significance is determined according to a risk of error of up to 5% (p-value < 0.05). For correlation measures, statistical analysis is considered for each pair of variables for which data are available (pairwise case exclusion). If there is too much information loss due to missing values, the aim is to obtain information about the missing values afterwards (e.g. by telephone interviews or document review). The data analysis is performed with IBM SPSS Statistics (version 25.0 or higher).

10. Information of risk assessment

10.1. Benefit-risk assessment

For this study, patient data is used that is generated during the regular medical, therapeutic and nursing care with assistive devices, therapies, medicines and nursing care. Any kind of additional medical, nursing and therapeutic intervention is omitted, which means that no medical risk to the patient is to be expected as a result of this study. Study-specific invasive examination methods are also neither planned nor required. Likewise, the collection of tissue samples and the testing of drugs are not planned. Therefore, the risk for participation in this study is considered to be very low.

10.2. Benefit

The study aims to evaluate data from patients with chronic neurological diseases regarding the provision of assistive devices, therapies, medicines, and care. The data describe the current reality of medical care. The results are used for the development of future care guidelines and treatment standards, which are created by medical societies. The aforementioned development of care guidelines and treatment standards can benefit patients with chronic neurological diseases in a disease group-specific manner.

10.3. Risks and burdens for the study participants

The time required for participation in the study is considered to be low. Participation in the study requires a preoccupation with the underlying neurological disease, which can result in a psychologically stressful situation. This risk is considered to be very low, since the issues are also addressed within regular care. In the unlikely event of a burden due to participation in patient surveys, study participation can be terminated at any time.

11. Information on data protection

11.1. Data protection

11.1.1. Data acquisition, data storage and data processing

The data of the registry study are collected by qualified staff of the APST and the participating study centers by means of data collection sheets or with the software of the APVP. Data collected by means of data collection sheets will be transferred to the APVP in a further work step by suitable personnel. The APVP data are stored and processed on a protected, SSL-encrypted server at Charité – Universitätsmedizin Berlin. The data is evaluated using suitable computer software and checked for plausibility and consistency. Data that is not plausible or missing is corrected or supplemented after checking. To process the data, the APST uses the computer center and the information technology infrastructure of the Charité. For this purpose, a contract of commissioned data processing according to DSGVO was concluded between APST and Charité.

11.1.2. Agreements on data protection and shared responsibilities

The APST ensures that data protection and data security requirements are met. Separate agreements on data protection are concluded for scientific cooperation with research institutions, in particular with medical faculties. In these, the contractual partners undertake to take the necessary data protection measures in good time to ensure data protection and, in cases of doubt, to involve the bodies responsible for data protection control (in the public sector, the state data protection commissioners and the federal data protection commissioner, otherwise the company data protection officers), as well as to comply with all applicable data protection regulations, in particular the Federal Data Protection Act, the applicable state data protection laws, and the basic data protection regulation (EU) 2016/679. The contracts shall regulate the joint responsibilities of APST and the cooperating research institutions within the meaning of Art. 26 of the GDPR.

11.1.3. Disclosure of pseudonymized data for research purposes

The data of the test persons are passed on by the APST - on the basis of an informed consent of the patient – for medical research purposes to research institutions. The transfer is based on contracts for scientific cooperation with research institutions, in particular with medical faculties. For this purpose, the data are pseudonymized (***Figure 2***). Pseudonymized subject data is information that can no longer be attributed to a specific data subject without the addition of further information, provided that this additional information is stored separately and is subject to technical and organizational measures to ensure that the personal data cannot be attributed to an identified or identifiable natural person (Art. 4 No. 5 GDPR).

11.1.4. Disclosure of anonymized data for research purposes

The data of the test persons are passed on by the APST – on the basis of an informed consent of the patient – for medical research purposes to researching pharmaceutical companies, medical technology companies, and project executing agencies of the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) as well as to scientific publishers for the purpose of publication. The data is passed on the basis of contracts for the secondary use of existing data with the companies or public institutions and on the basis of usage agreements with scientific publishers (***Figure 2***). For this purpose, the data are completely anonymized. Anonymized subject data is information that cannot be related to an identified or identifiable natural person (EG 26 p. 5 GDPR).

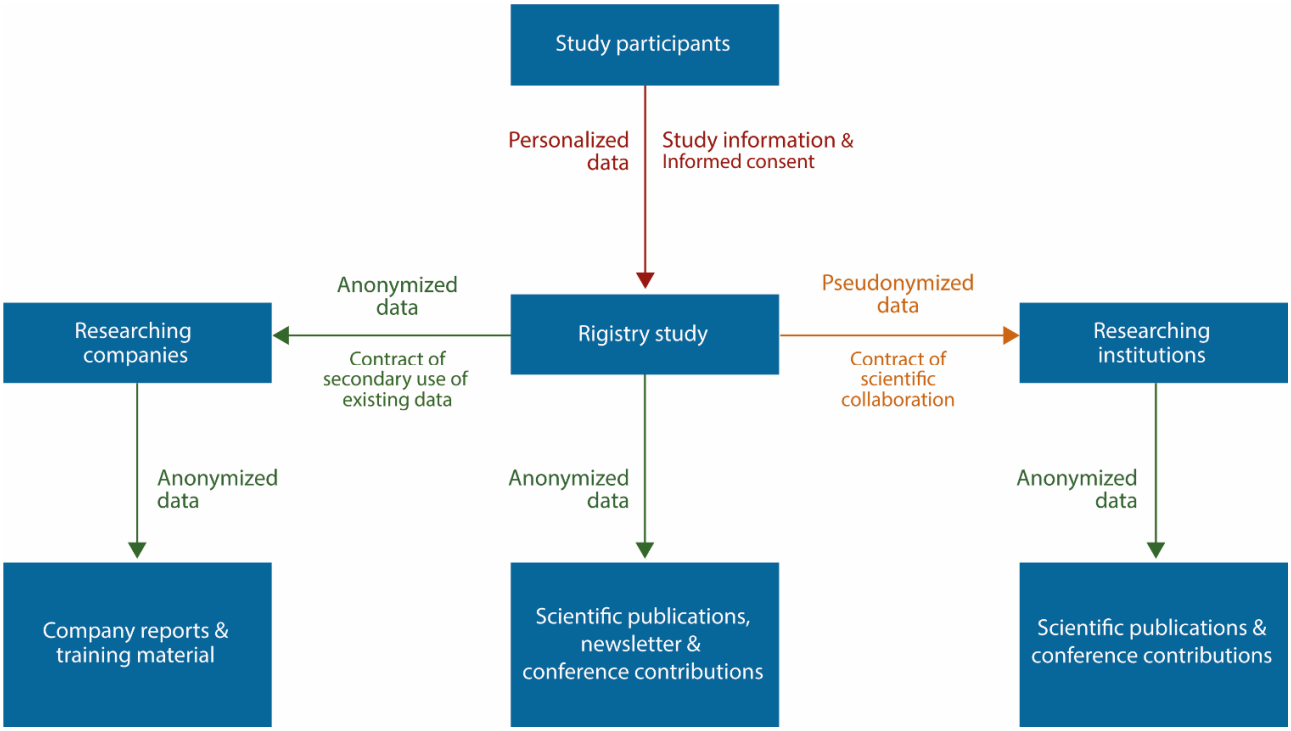

Figure 2: Sharing anonymized and pseudonymized data for research purposes.

11.2. Rights of data access

The registry study is conducted on behalf of Ambulanzpartner Soziotechnologie APST GmbH (APST) in cooperation with Charité – Universitätsmedizin Berlin. Both cooperation partners are recipients of the data:

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Charité – Universitätsmedizin Berlin
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11.3. Encryption of data

For further processing and statistical evaluation, the patient-related data are stored in accordance with § 3 (6) of the BDSG (Bundesdatenschutzgesetzt, Federal Data Protection Act). For pseudonymization, the data is given a code and thus protected by a patient ID. The ID is generated electronically.

11.4. Access to identifying data

Re-identification is only possible through access to the database. Such access and thus access to the source data and the patient ID is only available to persons who belong to the respective study center and are directly involved in the care.

11.5. Privacy policy

The collected and stored data are treated confidentially. Any transmission of data for statistical evaluation is encrypted and pseudonymized. An external and certified data protection officer has been appointed to monitor and ensure compliance with data protection at APST:

Hans-Christian Widegreen
Managing Director Widegreen&Data GmbH
Wrangelstraße 5, 10997 Berlin
E-mail: datenschutz@ambulanzpartner.de

11.6. Information, objection and deletion options:

Participants in the registry study have the right to view all data collected about them for the purpose of the study. In doing so, they will have the option of having an internet-based access to the Outpatient Partner Portal (APVP) set up for them or a person authorized by them. Alternatively, participants will be given the option to receive a printout of all data that has been entered on the APVP. Patients have the right at any time to point out possible errors in the recorded data and to request that the data be corrected.

The patient's consent to the registry study is valid indefinitely and post-mortem – as long as it has not been revoked by the patient or a legal successor of the patient. It is the justification for an unlimited processing of the data of the registry study. Patients can revoke their consent at any time without giving reasons. In the event of withdrawal of consent to study participation, all data will be destroyed at the patient's request and electronic data deleted in accordance with current technical standards. Access to the data is no longer possible.
Study participants have the right and opportunity to ask questions about study matters to the study director. Questions about the study may be directed to the following contact person:

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12. Financing information

The financing of the study is ensured by the Ambulanzpartner Soziotechnologie APST GmbH. It is financed by the basic funding of APST, by research funding of the Federal Ministry of Education and Research (BMBF) and by revenues from the secondary use of existing data. For the secondary use of existing data, contracts have been concluded with researching pharmaceutical companies and medical technology companies.

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14. Annex Directory

14.1. Appendix 1: Overview of the variables of all modules

Variables	Digit-Care	Digit-MIE	Digit-Robot	Digit-Thera	Digit-SiALS	Digit-THC	Digit-BoNT	Digit-SMA	Digit-PEG
Basic data (demographical and clinical data)	●	●	●	●	●	●	●	●	●
Data on the provision of assistive devices	●	●	●	●			●	●	●
Data on the provision of therapies	●								
Data on the provision of nutrition	●								
Data on the provision of medicines	●				●	●	●	●	●
Data on the provision of care								●	
Application behaviour and user experience data			●	●				●	●
ALS-Functional Rating Scale revised (ALSFRS-r)		●		●	●				●
ALS-Functional Rating Scale extendd (ALSFRS-Ex)			●					●	
SMA-Functional Rating Scale (SMA-FRS)								●	
Nummeric Rating Scale (NRS)		●		●		●			
Net Promotor Score (NPS)			●	●	●	●	●	●	●
Treatment Satisfaction Questionnaire for Medication (TSQM-9)						●	●	●	
King's stage						●			
Functional Ambulation Categories (FAC)								●	
Quality of Life and Socio-medical Characteristics								●	

Figure 3: Overview of the variables of the individual modules. *The basis for participation in the registry study is the Digit Care module, which collects the basic data on care. The differences to the other modules are shown in a table and include all other parameters collected.*