Deliverable

D4.4 Registry Manual

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Diffusion: Public

Staff functions and tasks

Person	Role	Contact
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	Registry Coordinator	ern-rnd-registry@med.uni-tuebingen.de

Data base structure and location

The data will be stored on servers of the central data-center of the Universitätsklinikum Tübingen (UKT) in the browser based, metadata-driven electronic data capture software database REDCap (Research Electronic Data Capture). The presentation layer (frontend) of the database is in the demilitarized zone (DMZ). This is a perimeter network which protects the clinics internal local-area network from untrusted traffic. This adds an additional layer of security to the network. The data access layer (backend) database is in the clinic network.

Data tranfer procedures

Data entry: The data will be provided for each disease group by the respective ERN-RND member hospitals coordinators as an Excel file that will be uploaded in the cloud of the coordinating center University Hospital Tübingen (UKT) Cloud (private cloud physically located at and administered by UKT).

Data export: The fully pseudonymised dataset will be exported once a year as an Excel file that is made accessible by the coordinators of each specialist center who contributes to the ERN-RND registry. To this end the dataset will be provided once a year in a protected folder of the UKT cloud for a limited amount of time (one week). Coordinators of all ERN-RND health care providers will get access to this folder to download the file. Each coordinator needs to confirm a priori with its local institutional review board the issues of data storage. This is part of the local project plan, patient information and consent that is premise for data entry.

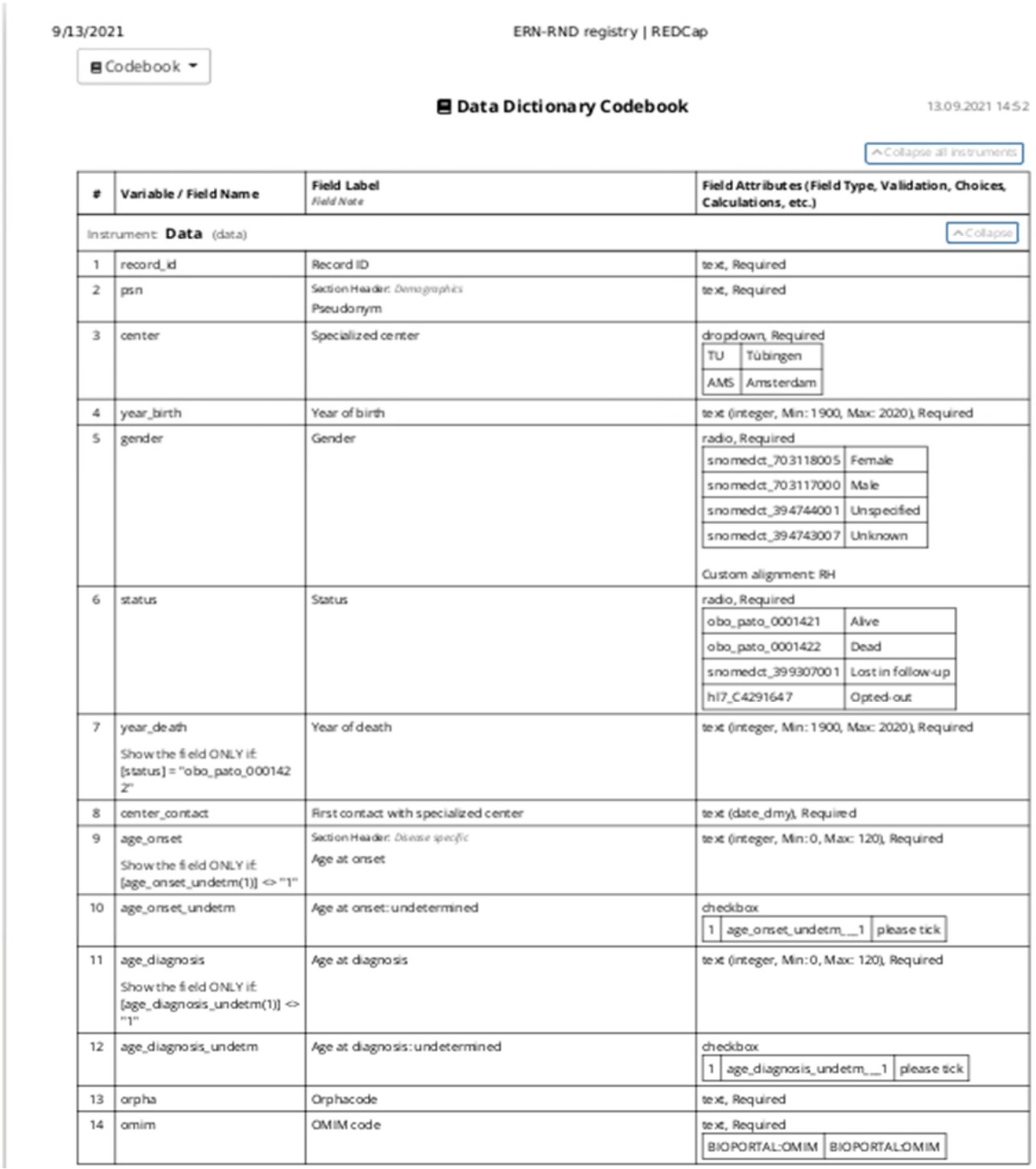
Definition of data points included in the registry

DATA	DESCRIPTION
ERN-RND center	The coordination office maintains a list of abbreviations for each health care provider within the ENR-RND. This enables the allocation of datasets to a specialized center for requests on more detailed information
Pseudonym	For data protection reasons the information should be pseudonymised, coded with numbers, letters or a combination of both. It is required that the patient has the same pseudonym the following years.
Year of Birth	For confidentiality reasons the registry will restrict the information only to Year of birth. It is important not to detail the Date of birth.
Sex	This item is essential for the assessment of sex specific aspects of the diseases. (i) female: snomedct_703118005, (ii) male:snomedct_703117000, (iii) unspecified:snomedct_394744001, (iv) unknown:snomedct_394743007
Patients status	To clarify the accessibility to patient's information is needed if patients are (i) alive: obo_pato_0001421, (ii) dead: obo_pato_0001422, (iii) lost in follow-up: snomedct_399307001, (iv) opted-out: hl7_C4291647
Year of Death	For confidentiality reasons the registry will restrict the information only to Year of death. It is important not to detail the Date of death. This data is required to evaluate the survival of patients with a specific disease.
First contact with specialised centre	This data is needed to inform on availability of longitudinal data in retrospective.
Age of onset	This data is essential information in the course of the disease.
Age at diagnosis	This data is required to assess delay in diagnosis. One goal of ERN RND is to reduce the time to diagnosis.
Orpha code	Orpha code is an internationally accepted diagnostic standard for the specification of rare diseases. It helps for an uniform nomenclature on disease entities and can be found at the following address: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=DE

OMIM code	The Online Mendelian Inheritance in Man (OMIM) provides an internationally accepted coding system for genetic diseases. It can be found at the following address: https://www.omim.org/
HPO terms	The Human Phenotype Ontology (HPO) provides lists of internationally accepted key features for the description of phenotype in a standardized way. It can be found at the following address: https://hpo.jax.org/app/
Agreement	This item provides information whether the patient agrees to be contacted for research purposes. It is categorized as (i) yes: obo_ncit_C49488 or (ii) no: obo_ncit_C49487. This is necessary data for the reassessment of patients.
Consent	Patient consent is indispensable for the inclusion of pseudonymized data in the registry. This data point must be “yes: obo_ncit_C49488” as otherwise no data is allowed to be entered into the registry. (No: obo_ncit_C49487)
Biological sample	This data is principle information on availability of biomaterial of any type (blood, urine, CSF, etc.) as it is important e.g. for genetic studies or biomarker aspects. It is categorized as (i) yes: obo_ncit_C49488 or (ii) no: obo_ncit_C49487.
Link to a biobank	If there are biological samples available, here should be a hyperlink to the biobank where the samples are stored. This information is essential to apply for biomaterials e.g. for genetic studies or biomarker development.
Classification of disability	Disease group specific scores provide essential information for the stratification of patients according to disease severity e.g. for inclusion in interventional trials

Data Plausibility Checks

To optimize the quality of the registry we implemented data plausibility checks. For all quantitative variables windows of plausibility there is defined and entered values checked upon saving. If the submitted data files will contain values outside the plausible range, the upload procedure will be interrupted, so that the incorrect filed cannot be saved. Fig. 1 presents the Data Dictionary Codebook, which describes what data will be accepted.



9/13/2021 ERN-RND registry | REDCap

Codebook

Data Dictionary Codebook 13.09.2021 14:52

Collapse all instruments

#	Variable / Field Name	Field Label *Field Note*	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: **Data** (data)			Collapse
1	record_id	Record ID	text, Required
2	psn	Section Header: *Demographics* Pseudonym	text, Required
3	center	Specialized center	dropdown, Required TU, Tübingen AMS, Amsterdam
4	year_birth	Year of birth	text (integer, Min: 1900, Max: 2020), Required
5	gender	Gender	radio, Required snomedct_703118005, Female snomedct_703117000, Male snomedct_394744001, Unspecified snomedct_394743007, Unknown Custom alignment: RH
6	status	Status	radio, Required obo_pato_0001421, Alive obo_pato_0001422, Dead snomedct_399307001, Lost in follow-up hl7_C4291647, Opted-out
7	year_death Show the field ONLY if: [status] = "obo_pato_0001422"	Year of death	text (integer, Min: 1900, Max: 2020), Required
8	center_contact	First contact with specialized center	text (date_dmy), Required
9	age_onset Show the field ONLY if: [age_onset_undetm(1)] <> "1"	Section Header: *Disease specific* Age at onset	text (integer, Min: 0, Max: 120), Required
10	age_onset_undetm	Age at onset: undetermined	checkbox 1, age_onset_undetm___1, please tick
11	age_diagnosis Show the field ONLY if: [age_diagnosis_undetm(1)] <> "1"	Age at diagnosis	text (integer, Min: 0, Max: 120), Required
12	age_diagnosis_undetm	Age at diagnosis: undetermined	checkbox 1, age_diagnosis_undetm___1, please tick
13	orpha	Orphacode	text, Required
14	omim	OMIM code	text, Required BIOPORTAL:OMIM, BIOPORTAL:OMIM

15	hpo_terms	HPO terms	dropdown, Required HP_0001251 | Ataxia 0001251 HP_0001258 | Spastic paraplegia 0001258 HP_0001332 | Dystonia 0001332 HP_0012675 | NBIA 0012675 HP_0007166 | Paroxysmal dyskinesia 0007166 HP_0002072 | Chorea 0002072 HP_0001300 | Parkinsonism 0001300 HP_0002145 | FTD 0002145 HP_0002415 | Leukodystrophy 0002415
16	contact_research	Section Header: *Other* Contact for research	radio, Required obo_ncit_C49488 | Yes obo_ncit_C49487 | No Custom alignment: RH
17	consent_reuse	Consent for reuse of data	radio, Required obo_ncit_C49488 | Yes obo_ncit_C49487 | No Custom alignment: RH
18	biosamples	Biological samples available	radio, Required obo_ncit_C49488 | Yes obo_ncit_C49487 | No Custom alignment: RH
19	biobank Show the field ONLY if: [biosamples] = "obo_ncit_C49488"	Biobank URL	text, Required
20	disability	Classification of disability	text (number_comma_decimal)
21	data_complete	Section Header: *Form Status* Complete?	dropdown 0 | Incomplete 1 | Unverified 2 | Complete

Fig. 1: Data Dictionary Codebook

Governance and policies

As illustrated below, the ERN-RND Registry project will be embedded in the management structure of the ERN-RND project to make use of the synergies, save cost and avoid the emergence of parallel structures.

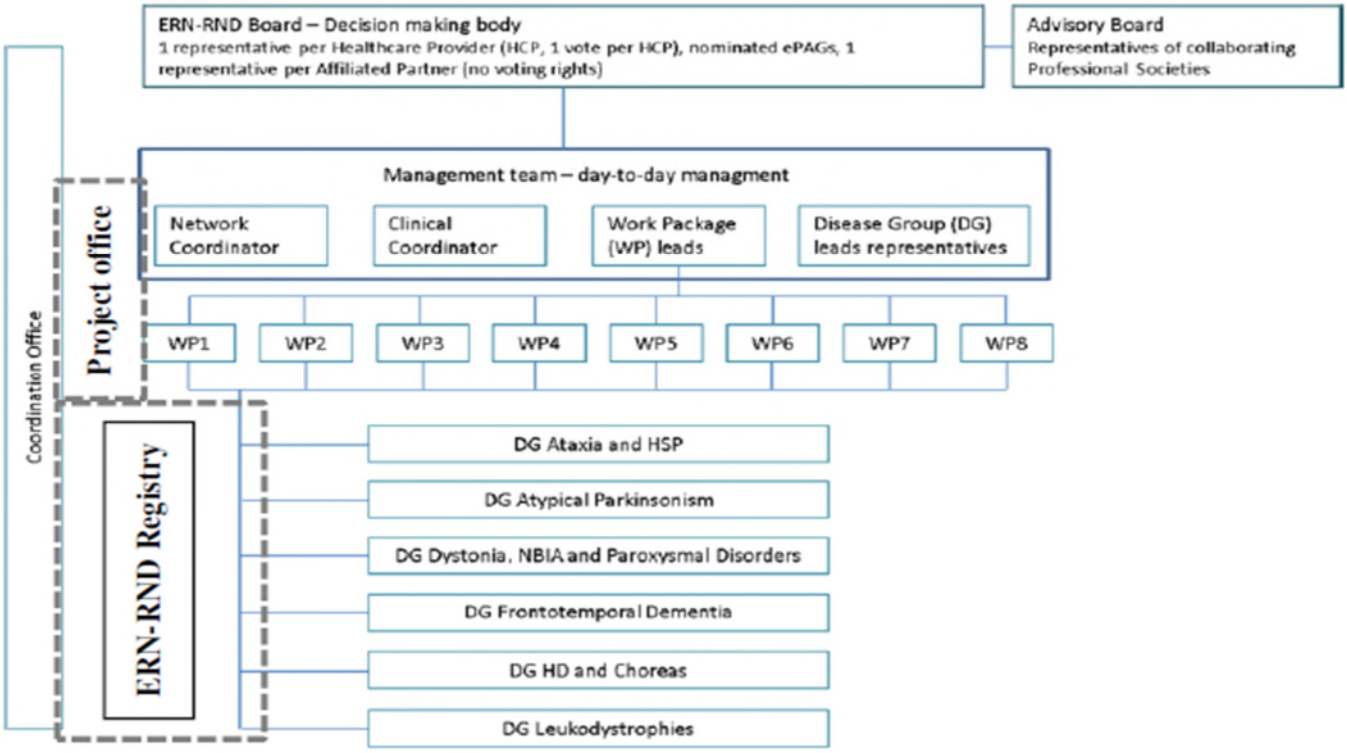


Fig. 2: Governance structure of ERN-RND. The integration of the registry project is highlighted.

Data protection aspects incl. Technical and organizational measures (TOMS)

The technical and organizational measures detailed below elucidate the important steps to assure the safety of the data that is captured for the registry.

Technical and organizational measures According to Art.32 DSGVO, § 3 LDSG

Required level of protection	High
Processing location(s)	REDCap
Documentation Type, Location	IT security concept of the UKT IT security concept for processing see IT security and operation concept meDIC TOMs HIH / CIN Operating concept REDCap

Technical/Organizat. Measures for Pseudonymization, Encryption	The pseudonymization of patient data takes place in the individual ERN centers.
Technical/Organizat. Measures for Availability, Resilience, Recoverability	Concept for data backup according to operating concept RZ UKT Failure tolerance & availability HIH / CIN
Technical/Organizat. Measures for Authenticity Traceability	UKT: Logging logins Logging accesses Logging data changes Processing documentation Authorization concept HIH: Own HIH-REDCap user administration for ERN-RND
Technical/Organizat. Measures for Confidentiality, Integrity	Access security own server rooms Access security workrooms Locked doors during absence
	Network/system access security Qualified firewall between UKT network and Internet Only defined/controlled network and system accesses Automatically or manually triggered screen lock when client is not in use/removed from workstation
	Authorization concept/s: Operating / authorization concept HIH Other persons do not have access to the data due to the role and authorization concept.
	Integrity Only tested programs/applications (REDCap) Data check by monitors convertible/possible

Prüfverfahren Art. 32 Abs. 1 d DSGVO	Annual review of the technical/org. Measures in the project

Ethical aspects and informed consent

The regulatory requirement for the data transmission to the ERN-RND Registry was assessed by the ethics committee approval given in Fig.3

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nachrichtlich:
Herrn Prof. Dr. med. Thomas Gasser

237/2020BO1	02.12.2020	27.01.2021
unsere Projekt-Nummer	eingegangen am	Datum

European registry on Rare Neurological Diseases (ERN-RND registry).
Hier:
Schreiben vom 01.12.20, CD mit den Unterlagen, Projektplan Version 1.4, Patientenaufklärung und Einwilligung für Erwachsene Studienteilnehmer Version 1.3, Patientenaufklärung und Einwilligung f. Jugendliche Version 1.3, Patientenaufklärung und Einwilligung f. Kinder Version 1.3, Stellungnahme des Datenschutzbeauftragten, Datenverarbeitungsverzeichnis, Datenschutzfolgeabschätzung, TOM Data sharing agreement (jew. m. sichtbaren Änderungen)

Sehr geehrter Herr Professor Schöls,

Ihr Schreiben mit den Kommentaren zum Schreiben der Ethik-Kommission vom 04.05.2020 sowie die geänderten und ergänzten Studienunterlagen haben der Ethik-Kommission an der Medizinischen Fakultät und am Universitätsklinikum Tübingen erneut zur Beratung vorgelegen.

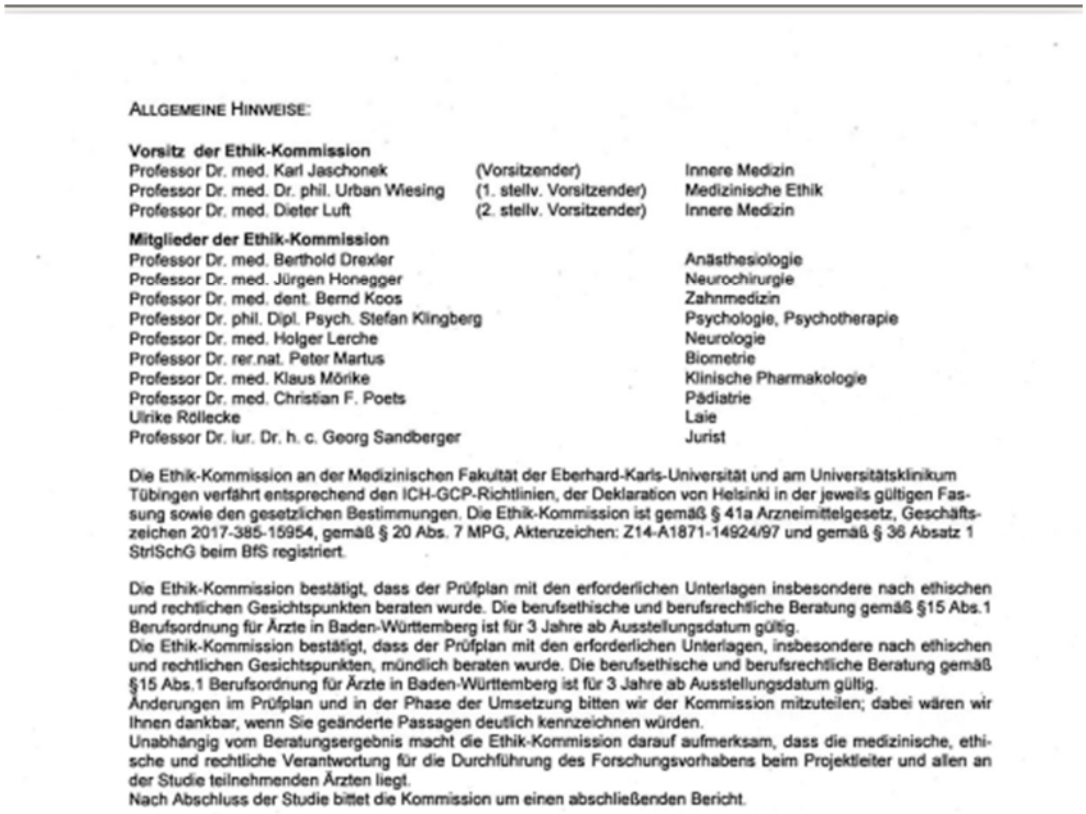
Danach bestehen gegen das von Ihnen geplante Register seitens der Kommission keine Bedenken.

Die Ethik-Kommission bedankt sich für Ihre sehr ausführlichen Kommentare, insbesondere zur Frage 4 zum Prüfplan und möchte Sie bitten, das endgültige Statut nach seiner Fertigstellung der Ethik-Kommission zur Vervollständigung des Antrags nachzureichen.

Für die Durchführung der Studie wünschen wir Ihnen viel Erfolg.
Mit freundlichen Grüßen

Prof. Dr. med. Dieter Luft
Stellv. Vorsitzender der Ethik-Kommission

Seite 2: Allgemeine Hinweise



ALLGEMEINE HINWEISE:

Vorsitz der Ethik-Kommission

Professor Dr. med. Karl Jaschonek	(Vorsitzender)	Innere Medizin
Professor Dr. med. Dr. phil. Urban Wiesing	(1. stellv. Vorsitzender)	Medizinische Ethik
Professor Dr. med. Dieter Luft	(2. stellv. Vorsitzender)	Innere Medizin

Mitglieder der Ethik-Kommission

Professor Dr. med. Berthold Drexler	Anästhesiologie
Professor Dr. med. Jürgen Honegger	Neurochirurgie
Professor Dr. med. dent. Bernd Koos	Zahnmedizin
Professor Dr. phil. Dipl. Psych. Stefan Klingberg	Psychologie, Psychotherapie
Professor Dr. med. Holger Lerche	Neurologie
Professor Dr. rer.nat. Peter Martus	Biometrie
Professor Dr. med. Klaus Mörike	Klinische Pharmakologie
Professor Dr. med. Christian F. Poets	Pädiatrie
Ulrike Röllecke	Laie
Professor Dr. iur. Dr. h. c. Georg Sandberger	Jurist

Die Ethik-Kommission an der Medizinischen Fakultät der Eberhard-Karls-Universität und am Universitätsklinikum Tübingen verfährt entsprechend den ICH-GCP-Richtlinien, der Deklaration von Helsinki in der jeweils gültigen Fassung sowie den gesetzlichen Bestimmungen. Die Ethik-Kommission ist gemäß § 41a Arzneimittelgesetz, Geschäftszeichen 2017-385-15954, gemäß § 20 Abs. 7 MPG, Aktenzeichen: Z14-A1871-14924/97 und gemäß § 36 Absatz 1 StrlSchG beim BfS registriert.

Die Ethik-Kommission bestätigt, dass der Prüfplan mit den erforderlichen Unterlagen insbesondere nach ethischen und rechtlichen Gesichtspunkten beraten wurde. Die berufsethische und berufsrechtliche Beratung gemäß §15 Abs.1 Berufsordnung für Ärzte in Baden-Württemberg ist für 3 Jahre ab Ausstellungsdatum gültig.
Die Ethik-Kommission bestätigt, dass der Prüfplan mit den erforderlichen Unterlagen, insbesondere nach ethischen und rechtlichen Gesichtspunkten, mündlich beraten wurde. Die berufsethische und berufsrechtliche Beratung gemäß §15 Abs.1 Berufsordnung für Ärzte in Baden-Württemberg ist für 3 Jahre ab Ausstellungsdatum gültig.
Änderungen im Prüfplan und in der Phase der Umsetzung bitten wir der Kommission mitzuteilen; dabei wären wir Ihnen dankbar, wenn Sie geänderte Passagen deutlich kennzeichnen würden.
Unabhängig vom Beratungsergebnis macht die Ethik-Kommission darauf aufmerksam, dass die medizinische, ethische und rechtliche Verantwortung für die Durchführung des Forschungsvorhabens beim Projektleiter und allen an der Studie teilnehmenden Ärzten liegt.
Nach Abschluss der Studie bittet die Kommission um einen abschließenden Bericht.

Fig. 3: Screenshot of the ethics approval from University Hospital Tuebingen

List of participating centres

1. Universitätsklinikum Tübingen, Germany
2. Motol University Hospital, Czech Republic
3. Universitätsklinikum Schleswig-Holstein, Germany
4. Klinikum der Universität München, Germany
5. VU University Medical Center Amsterdam, Netherlands
6. AO di Padova, Italy
7. Complejo Hospitalario Regional Virgen del Rocío, Spain
8. Eginitio Hospital, National and Kapodistrian University of Athens, Greece
9. Ghent University Hospital, Belgium
10. CHU de Toulouse, France

11. Universitätsklinikum Ulm, Germany
12. Semmelweis University, Hungary
13. University of Pécs, Hungary
14. Stichting Katholieke Universiteit, doing business as Radboud University Medical Center Nijmegen, Netherlands
15. University Hospital in Krakow, Poland
16. Hospital Clínic i Provincial de Barcelona y Hospital de Sant Joan de Déu, Spain
17. Hospital Universitari Vall d'Hebron, Spain
18. Center for Pediatric Rare Neurological Diseases / Dpt. of Pediatrics, Medical University of Vienna, Austria
19. Centre Hospitalier du Luxembourg
20. Rigshospitalet Copenhagen, Denmark
21. Aarhus Universitets Hospital, Denmark
22. Antwerp University Hospital, Belgium
23. Aorn A. Cardarelli, Italy
24. AOU Pisana, Italy
25. Azienda USL di Bologna - IRCCS Istituto delle Scienze Neurologiche, Italy
26. Fakultní nemocnice U Sv. Anny v Brně, Czech Republic
27. Hannover Medical School, Germany
28. Hospital General Universitario Gregorio Marañón, Madrid, Spain
29. Hospital Universitario Marqués de Valdecilla, Italy
30. Institute of Psychiatry and Neurology, Warsaw, Poland
31. Karolinska Universitetssjukhuset, Stockholm, Sweden
32. Katholisches Klinikum Bochum, Germany
33. Leiden University Medical Center, Netherlands
34. Maastricht University Medical Center, Netherlands
35. Sahlgrenska Universitetssjukhuset, Sweden
36. Szent-Györgyi Albert Medical Center, University of Szeged, Hungary
37. Tallaght University Hospital, Ireland
38. The Cyprus Foundation for Muscular Dystrophy Research (The Cyprus Institute of Neurology and Genetics), Cyprus

39. University Hospitals Leuven, Belgium
40. Thomayer Hospital, Prague, Czech Republic
41. General University Hospital in Prague, Czech Republic
42. Hospital Clinico San Carlos, Madrid, Spain
43. Hospital Universitario Central de Asturias, Spain
44. Hospital Universitario La Paz, Madrid, Spain
45. Pia Fond. "Card. G. Panico", Lecce, Italy
46. CHU de Toulouse, France
47. Universitätsklinikum Aachen, Germany
48. Universitätsklinikum Würzburg, Germany
49. IRCCS Clinical Institute Humanitas – Rozzano, Italy
50. Foundation IRCCS neurological institute Carlo Besta – Milan, Italy
51. Université libre de Bruxelles, Belgium
52. University Neurological Hospital “St. Naum” Sofia, Bulgaria
53. Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, France: Reference Centre for Rare Diseases 'Neurogenetics', France
54. Universitätsklinikum Bonn, Germany
55. Pediatric hospital Bambino Gesù, Rome, Italy
56. AOU Siena, Italy
57. Vilnius University Hospital Santariškių Klinikos, Lithuania
58. University Medical Center Groningen, Netherlands
59. Erasmus MC: University Medical Center Rotterdam, Netherlands,
60. University Medical Centre Ljubljana, Slovenia
61. Center for Rare Movement Disorders / Dpt. of Neurology, Medical University Innsbruck, Austria
62. Klinički bolnički centar Zagreb, Croatia
63. Pauls Stradins Clinical University Hospital, Riga, Latvia
64. Oulu University Hospital (OUH), Finland
65. Tartu University Hospital, Estonia
66. National Coordination Hub, Mater Dei Hospital (MDH), Malta
67. AOU Policlinico Bari, Italy

68. Azienda Ospedaliera Universitaria Federico II, Italy
69. Assistance Publique-Hôpitaux de Paris, Hôpital Henri-Mondor, France: Reference centre for Huntington's disease, France
70. Assistance Publique-Hôpitaux de Paris, Hôpital Robert-Debré, France: Reference centre for Leukodystrophies, France
71. Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, France: Reference centre for rare dementias, France