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Rare Diseases

- Affect fewer than 1:2000, most fewer than 1:100 000
- More than 7000 rare diseases affect 5-8% of global population
- In Switzerland, an estimated ½ Mio individuals affected
- Mostly of genetic origin
- Often life-threatening or chronically debilitating
- Lack of effective therapies and interventions
- Diagnostic odyssey
- Heavy burden for patients and caregivers

Rare Diseases

- Etiology and natural histories poorly understood
- Clinical and biological information fragmented
- Lack of relevant animal models
- Studies if available at all often poorly powered
- Interest from pharmaceutical industry limited
- Lack of standardized diagnostic and therapeutic regimens

→ large unmet medical need

Rare Diseases in Switzerland

- Rare disease patients not visible in routine statistics
- Lack of pan-rare-disease population-based registry

→ Lack of epidemiological data

Rare Diseases in Switzerland

- Small multi-language population with federalist health system, barred from participation in the EU public health initiatives
- Swiss centers not first choice (if included at all) for typical multi-center studies required for most studies and clinical trials in the field of rare diseases

→ Swiss RD patients not included in clinical trials

Rationale for a national, minimal rare disease registry

- To make rare disease patients **visible** in Switzerland
- To facilitate their **participation** in (international) clinical research and trials

Rationale for a national, minimal rare disease registry

- To make rare disease patients **visible** in Switzerland
- To facilitate their **participation** in (international) clinical research and trials
- Detailed rare disease registries (natural history studies, etc.) generally need to be international registries

Goals

- Registration of a minimal data set of (eventually all) patients with a diagnosed or suspected rare disease* residing in Switzerland in order to facilitate
- Assessment of the Swiss Rare Disease situation
 - epidemiology (incidence, prevalence, survival, mortality)
 - health care
- Participation of Swiss patients in national and international clinical studies

* Starting with patients with rare non-oncological diseases. Patients with rare cancers will already be registered under the Swiss National Law on Cancer Registration and might be included in a later step.

Barriers

- Patients are “rare” and scattered across disciplines
- Identification of patients via routine data is not possible, because ICD-10 does not code most rare diseases, making data sources such as mortality and hospitalization statistics non-evaluative; also, many of the patients are outpatients
- Voluntary registration → physicians’ motivation and hospital management’s support vital
 - Balance burden of data collection with quality and quantity of data collected

Key factors for success

- Ease of use
- Modalities for consent
- Framework for data linkage and data security
- Communication
- Participation of physicians, institutions, and patients

History

- Initiative for Swiss Rare Disease Registry 2013 by Prof. Dr. med. Matthias Baumgartner through radiz – Rare Disease Initiative Zurich, Clinical Research Priority Program University of Zurich
- Working group led by Prof. Dr. med. Claudia Kuehni, Institute of Social and Preventive Medicine (ISPM) in Bern and Prof. Dr. med. Matthias Baumgartner, Children's Hospital Zürich / UZH
- Permission from the “Eidgenössische Expertenkommission für das Berufsgeheimniss in der medizinischen Forschung” obtained in 2013 for collection of non-anonymous data

History

- Human Research Act since 2014, requiring adaptation of procedures
- Seed funding received from Gebert RUF Stiftung (50 k) to adapt concept and procedures
- National law on cancer registration and its ordinances stipulates possibility of financing further registries, possibly promising some sustainability
- Formation of larger working group and decision to consult wide range of stakeholder enabled through support from FOPH to develop concept (57.5 k)
- Application for new ethics approval with updated project planned for winter 2017

Working group

- Prof. Dr. med. Claudia Kuehni, ISPM Bern, University of Bern
- Prof. Dr. med. Matthias Baumgartner, Kispi Zurich and UZH
- Dr. med. Romain Lazor, CHUV
- Prof. Dr. med. Emanuel Christ, University Hospital Basel
- Dr. med. Sandra Bigi, Inselspital Bern
- Agnes Nienhaus, unimedswisse
- Dr. Adrian Spoerri, SwissRDL, ISPM Bern
- Rahel Kuonen, ISPM Bern
- Dr. Saskia Karg, Kispi Zurich
- Dr. Anne Tscherter, ISPM Bern

Stakeholders

Service providers for care, research, and teaching

- All hospitals, represented by H+
- University hospitals and their medical faculties, represented by Universitäre Medizin Schweiz
- Allianz Kinderspitäler der Schweiz (AllKids)
- Physicians and experts in the field, represented by the FMH and the respective professional associations

Stakeholders

Research institutions

- Swiss Academy of Medical Sciences (SAMS)
- State Secretariat for Education, Research and Innovation (SERI)
- Swiss National Science Foundation (SNSF)
- Swiss Ethics Committees on research involving humans (Swissethics)
- Swiss Clinical Trial Organisation (SCTO)
- Swiss Research Network of Clinical Pediatric Hubs (SwissPedNet)
- Swiss Personalized Health Network (SPHN) Initiative

Stakeholders

Federal and cantonal institutions

- Federal Office of Public Health (FOPH)
- Federal Statistical Office (FSO)
- Federal Social Insurance Office (FSIO)
- Schweizerische Konferenz der kantonalen Gesundheitsdirektoren und –direktorinnen (GDK) and the cantons
- eHealth Schweiz
- Expertenkommission für genetische Untersuchungen beim Menschen (GUMEK)

Stakeholders

Patient organisations and communities of interests

- ProRaris
- Orphanet
- Piattaforma Malattie Rare Svizzera Italiana
- IG Seltene Krankheiten

Stakeholders

Registry operators

- SwissPedRegistry
- SwissRDL

Stakeholders

Quality assurance and international technology

- Schweizerische Akademie für Qualität in der Medizin (SAQM)
- Nationaler Verein für Qualitätsentwicklung in Spitälern und Kliniken (ANQ)
- Vereinigung Gesundheitsinformatik Schweiz (VGIch)
- Swiss Institute of Bioinformatics (SIB)
- Schweizerische Union für Labormedizin (SULM)

Guiding documents

- Current legal framework for medical registries
- “National concept for rare diseases” and its implementation plan published by the FOPH
- Article 24 from the national law on cancer registration and its ordinance
- Joint recommendations for medical registries by SAMS, unimedswiss, H+, FMH, and ANQ
- Report “Patient Involvement in Establishment and Operation of Registries” by ProRaris

Guiding documents / international experience

- PARENT "Methodological guidelines and recommendations for efficient and rational governance of patient registries", 2015
- EPIRARE "Guidelines for data sources and quality for RD Registries in Europe ", 2014
- EUCERD Core Recommendations on rare disease patient registration and data collection, 2013
- EURORDIS-NORD-CORD Joint Declaration of 10 Key Principles for Rare Disease Patient Registries, 2012
- Experiences from other European pan-rare-disease population-based registries (Belgium, France, Italy, the Nordic countries, and Spain)

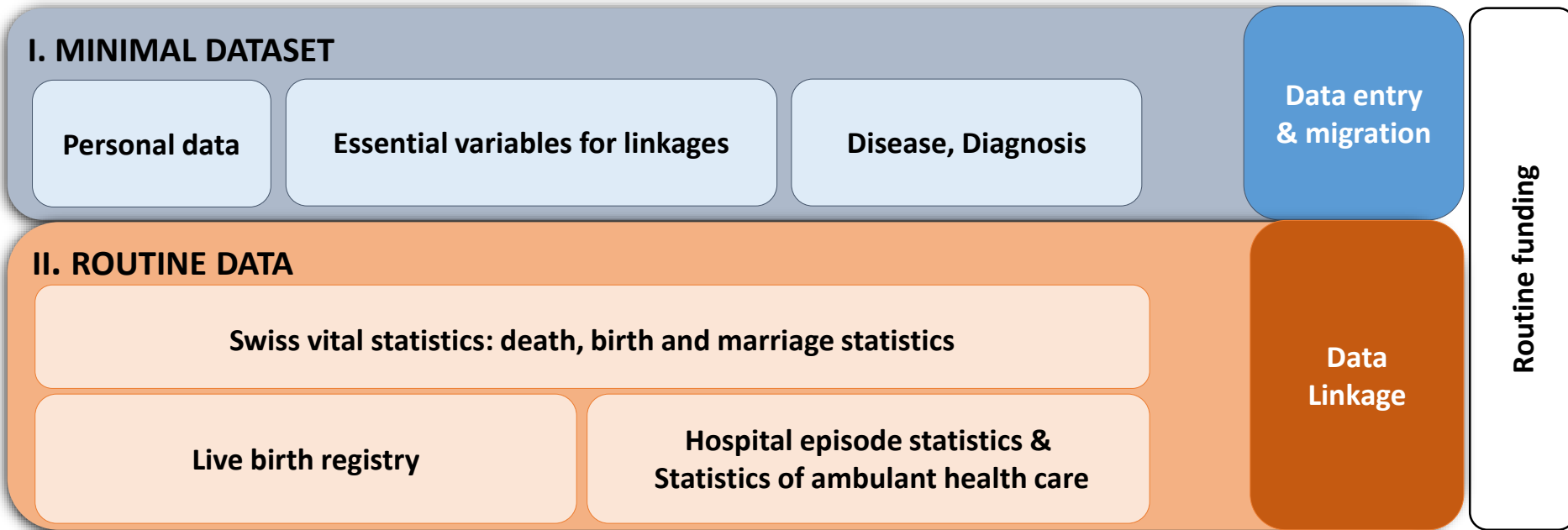
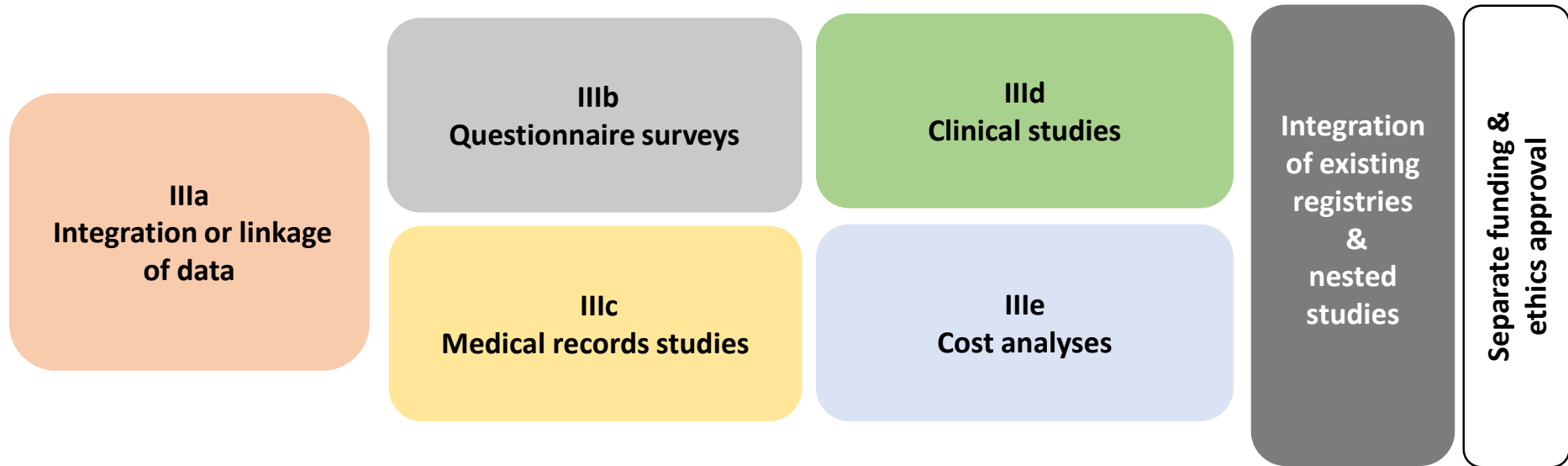
Other national pan-rare-disease registries

	Belgium	France	Italy	Nordic countries	Spain
Registration under auspices of	Minister of Public Health	French Ministry of Health	Italian Ministry of Health	Nordic Council of Ministers	Royal Decree
Patient's permission required	No	No for non-identifying information; Yes for personal information	No	No	No
Collects non-anonymized data	No name but SSN registered. SSN converted to a unique code.	Yes. SSN used for linkage studies.	Yes	Yes	Yes
National/regional coverage	National	National	National, but data collected on regional level	Covers 4 Nordic countries (Denmark, Finland, Norway, Sweden)	National
Funding	Public	Public	Public, on a regional level	Public	n/a

SRDR: Approach

Non-anonymous registry with minimal data set

- Names and addresses are essential
→ to invite patients into studies, and monitor survival
but identifying data are kept separate from medical data



Coding via the ORPHA code

- ICD-10 does not code most rare diseases
 - same disease → different codes
 - different diseases → same code
- SNOMED codes more rare diseases than ICD-10, but problem of ambiguity remains
- Code via gene (OMIM) → RD not all genetic, diagnosis known without knowing gene defect, different gene defects may cause same disease, would need to link back to disease → granularity
- ICD-11 is a long way off, but will allow linkage with ORPHA codes

Coding via the ORPHA code

- ORPHA codes are specific for rare diseases and are provided by Orphanet*
- Coding with ORPHA codes has successfully been piloted since 2015 in the CHUV and the HUG within their hospital information system, since 2016 also in the Children's Hospital Zurich
→ using this coding system is feasible

* established by the INSERM (French National Institute for Health and Medical Research) in 1997, European endeavor as of 2000, supported by European Commission, now consortium of 40 countries, within Europe and across the globe

Patient identification

- Notification by health care providers (hospitals, physicians, laboratories)
- Patient self-notification via dedicated platform in accordance with European and US-American initiatives*

* “Recommendation on rare disease Patient registration and data collection from the European Union Committee of Experts on Rare Diseases (EUCERD)” and NORD initiative

Minimal data set

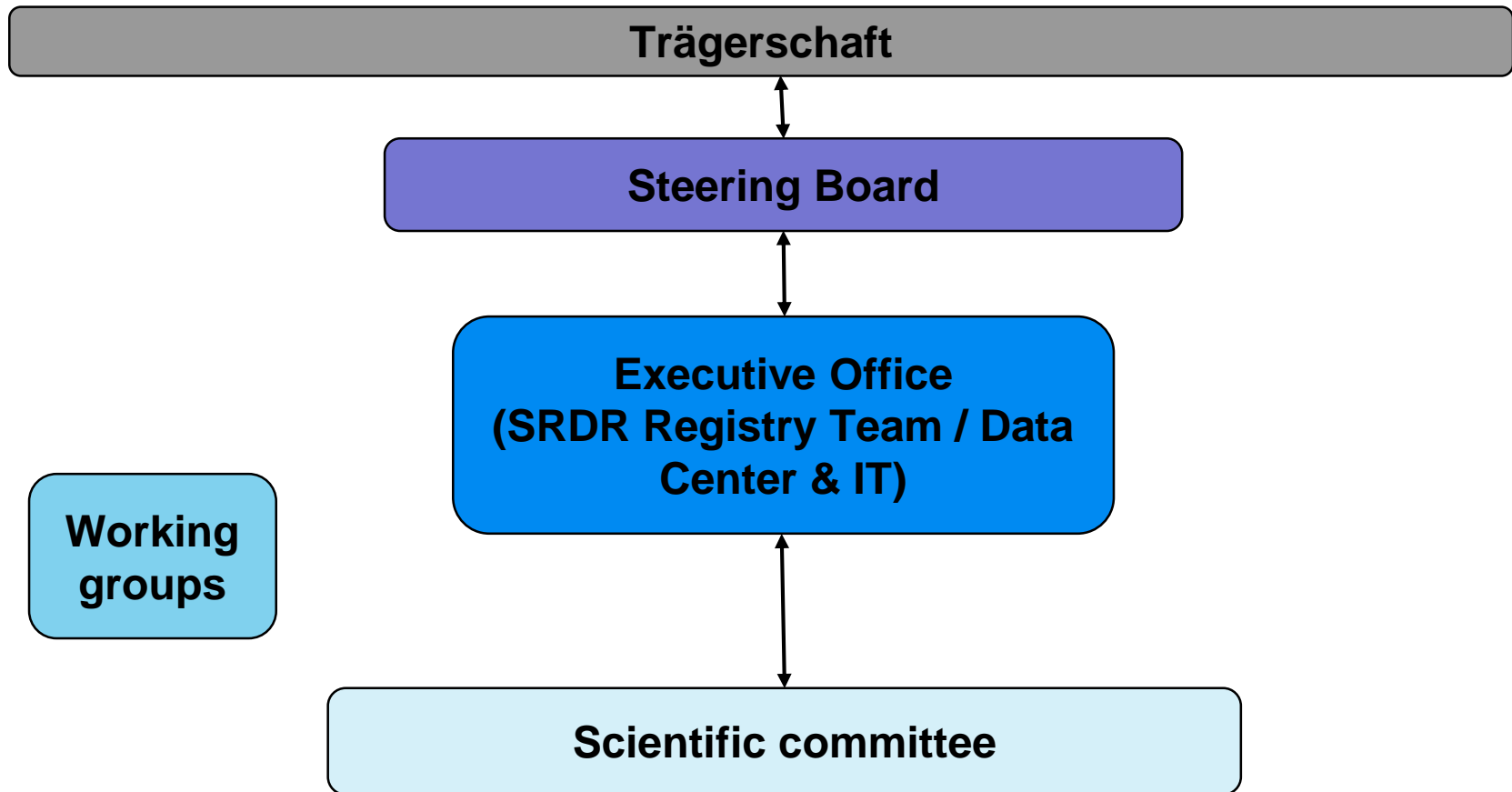
1. Personal data
2. Treating institution
3. Diagnosis / diagnoses
4. Mode of diagnosis
5. Age at onset of symptoms
6. Information status of patient

Consent

Registration of minimal data set without consent (opt-out option) vital for feasibility of registry due to

- Completeness requirement
- Lack of feasibility of providing true informed consent
- Favorable risk / benefit ratio
- International standard

Registry structure and governance



Sustainability

- contingent upon high level of acceptance, participation, and support
 - Acceptance, participation, and support contingent upon ease of use, feasibility for clinics, transparency, governance and communication
 - Ease of use and feasibility for clinics contingent upon ethics approval to proceed without active consent (opt-out option)

- contingent upon funding
 - Bridge funding required for registry from end 2017 until early 2019 in order to allow registry to potentially qualify for
 - Funding through CRL from 2019 onward; requires matched funding

Next steps

- Consultation by stakeholders
 - concept sent by June 15th
 - consultation until July 15th
- Approval rate of 80% required for submission of concept to FOPH
- Revision of concept based on stakeholder recommendations
- Submission of new ethics application based on revised concept
- Fundraising activities
- First stage of registry setup and data entry in 2018 (contingent upon bridge funding)



IVa Integration or linkage of data from existing small clinical registries or clinical studies

IVb Questionnaire surveys: collection of new data from patients and physicians

IVd Clinical studies: collection of new data involving patient examination

IVc Medical records studies: extraction of available data from medical records

IVe Cost analysis: using data from Disability Insurance and/ or Health Insurance

Integration of existing registries & nested studies

Separate funding & ethics approval

I. MINIMAL DATASET

Personal data

Essential variables for linkages

Disease, Diagnosis

Data entry & migration

Routine funding

II. ROUTINE DATA

Swiss Vital Statistics: death, stillbirth, birth and marriage statistics

Live birth registry

Hospital Episode Statistics and Statistics of ambulant health care

Data Linkage

III. Possible collaboration with the Swiss Biobank

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