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INTERDISCIPLINARY PLATFORM ON BENEFIT ASSESSMENT
Volume 10
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# What are the (additional) benefits of registry data?

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# Goals of the plattform

Since the introduction of AMNOG in 2011, Germany has a well-established and widely accepted „adaptive system" for the assessment of the patient-relevant additional benefit (Health Technology Assessment, HTA). The assessment of the additional benefit by the Federal Joint Committee (G-BA) is the result of expert work based on a law (AMNOG) and procedural and methodical regulations.

The active players on the side of the G-BA and the health insurance funds are classified as scientists, hospital physicians and office-based statutory health insurance physicians, the Medical Service of the Health Funds and employees of the insurance fund administration, but also as patient representatives, however, they act on the basis of their own interests. Value dossiers for new pharmaceuticals, likewise qualified and interest-based, are submitted to the G-BA by the pharmaceutical companies, which serve as the basis for the assessment of the additional benefit.

Because the supply of pharmaceuticals to the population is significantly influenced by the assessment of the additional benefit, it makes sense to provide critical and careful support for the assessment process with a focus on identifying possible faults and counteracting imbalances. The Interdisciplinary Platform on Benefit Assessment set itself the task of supporting the benefit assessment within a small group of experts with the following objectives:

- Discussing the procedures for the assessment of the additional benefit, including in relation to approval of pharmaceuticals,
- Working towards international standards of evidence-based medicine and of health economy being adhered to as well as applied and further developed,
- Determining whether and to what extent patient-relevant additional benefits, in particular in the areas of mortality, morbidity and quality of life, are identified and which methodological problems occur during the process,
- dentifying possible undesirable developments, in particular with regard to supplying patients with new active substances,
- Enabling and holding a constructive dialogue with all players involved in the benefit assessment procedure, e. g. on the further development of the legal framework conditions of AMNOG.

Moreover, the European perspective in HTA of innovative pharmaceuticals was reinforced by the European Commission's proposal for a Regulation on HTA in 2018. Monitoring the conflict between the well-established national assessment and the intended European HTA harmonisation is also a central concern of the platform. The Interdisciplinary Platform would like to make a contribution to ensuring that new active substances are transparently and fairly assessed. According to the Advisory Council, an interdisciplinary dialogue about the results of the assessment and the applied benefit assessment methods is essential. Furthermore, in the benefit assessment process it sees a good opportunity to inform the prescribing physicians of the expected additional benefits of new pharmaceuticals for patients earlier than it was previously the case.

The Interdisciplinary Platform is a result of the discussion process between clinicians and experts. The mutual desire to pool specialist knowledge in the form of interdisciplinary seminars is supported by an open consortium of sponsors. These include AbbVie Deutschland GmbH & Co. KG, DAK Gesundheit, MSD Sharp & Dohme GmbH, Novo Nordisk Pharma GmbH, Roche Pharma AG, Association of Research-Based Pharmaceutical Companies (vfa e.V.), and Xcenda GmbH.

**The Advisory Council of the Interdisciplinary Platform on Benefit Assessment**

# Confirmed benefit – but also an additional benefit? Registry data in the discourse

**By Professor Jörg Ruof**

Dear readers,

as you know, the scientific Advisory Council is responsible for the contextual orientation of the Interdisciplinary Platform on Benefit Assessment. During our discussion in the council about the title of this publication nobody doubted the high scientific „benefit" that can be generated from high-quality registry data.

However, it was not finally answered to what extent such data are, however, suitable to determine the „additional benefit" as compared to the current treatment standard – as requested by the AMNOG procedure. This open question is somehow paraphrased by putting the prefix „additional" into brackets in the title.

The content of this publication is closely connected with the expert discussion. The European Medicines Agency EMA has established the „Patient Registry Initiative" and elaborated principles for a „Good Registry Practice" in line with the „Good Clinical Practice" for clinical studies that also include specifications for several pathologies. In his article, Professor Mol outlines both background and perspectives.

Despite the increasing relevance of registry data, we don't have a national infrastructure here in Germany standardising and supporting scientific research by using registries. In his article, Professor Stausberg from the German Network for Health Services Research (DNVF e.V.) outlines the resulting partly redundant and often fragmentary developments. These limit the potential of high-quality registry data.

In May 2019, the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) commissioned the IQWiG to draw-up a report for the handling of treatment-related data within the scope of AMNOG procedures. This report was published in January 2020. Dr Behring's and Dr Lange's articles are closely connected with this project and the corre-

sponding „Rapid Report". For the IQWiG, a lower data quality in non-randomised studies than in high-quality clinical studies is not acceptable. Dr Behring illustrates the possibility of calling upon high-quality post-market data to create an extended decision basis for the benefit assessment – after other options such as the adaptation of study designs in the development program have been exhausted.

One focus of this publication and the associated platform meeting in October 2019 is the consideration and involvement of registries and registry experts, respectively. Three data collections were selected:

- Paediatric oncology registry dates by the example of Non-Hodgkin lymphoma study group (NHL-BFM),
- NeuroTransData Registry by the example of multiple sclerosis,
- SMArtCare Registry for spinal muscular atrophy (SMA).

All three registries have a broad scientific basis and have been well-established thus providing numerous impulses for the current discussion.

Thus, the NHL study group demonstrated significant improvements in the survival of children and adolescents suffering from various diseases on the basis of so-called therapy optimisation studies (TOS). The aim of the TOS is not to evaluate or approve individual pharmaceuticals, but rather to achieve a systematic and continuous improvement of the complex standard therapy. Thus, these are (vitally) important findings that can only partly be reflected in the evaluation according to Section 35a SGB V that is mainly set up as a single technology assessment.

The NeuroTransData Registry is also focussed on optimising the therapeutic strategy. Also due to the significantly higher number of patients the authors assume that data can be generated within the scope of these registries that can achieve a comparable standard to RCTs in terms of quality and robustness during the evaluation of e.g. individual pharmaceuticals. Against the background of constantly expanding therapeutic options for spinal muscular atrophy, the SMArtCare Registry is of particular importance. Highly-effective biological and gene therapeutic treatments open up completely new partly long-term therapeutic horizons that will become particularly challenging for the comparative benefit assessment.

Finally, in his article Professor Ullmann refers to the diverse possibilities emerging from high-quality registries for the optimised social healthcare (i.e. the ultimate goal) from the perspective of a politician with profound knowledge of the clinical research environment.

Registry studies can provide valuable treatment-related additions to RCT data with the potential to close evidence gaps where RCTs fail. The close national and European network, especially for very rare diseases, compliance with high quality standards, and use of diverse possibilities of the increasing digitalisation must be taken into consideration.

Although this publication is not a „registry of registries", we hope it provides a good overview of the current discussion about this topic from different perspectives.

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# Good Registry Practice – setting the context

**Prof Peter G. M. Mol, Department of Clinical Pharmacy and Pharmacology, University Medical Centre Groningen, University of Groningen; Dutch Medicines Evaluation Board, Utrecht, The Netherlands**

*The European Medicines Agency (EMA) experience with patient registries is extensive. Of 116 centrally approved medicinal products in Europe between January 2007 and January 2011; 43 marketing approval dossiers contained one to six registries/registry-based studies. In an effort to optimize the contribution of registries to the benefit-risk evaluation of medicines the EMA ‚Patient Registry Initiative' was launched. The Initiative started with an identification of registry guidance, and existing European registries that had been collected within the Cross Border PAtient REgistries iNiTiative (PARENT), a Joint Action under the EU's Health Programme 2008-2013. Data generated in clinical practice – including registry data – offers the possibility to address remaining regulatory questions at approval. Disease registries are favoured over product registries, but it is key that design, data source and analysis are fit for purpose. Acceptability of real world evidence is determined by the objective, i.e., safety and/or efficacy, and the role in regulatory decision-making. Higher standards are applied to studies and data sources (registries) – that are pivotal to decision-making rather than perform a supportive role.*

At time of approval the knowledge of drug effects – beneficial and harmful – is not complete. Post license evidence may be generated using Real World Data (RWD) to address remaining uncertainties on drug effectiveness and/or safety. These RWD are obtained from routine healthcare practice from sources such as electronic health records, insurance claims data and patient registries. At the European Medicines Agency (EMA) we use the following definition for patient registries; ‚organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time.'

Our experience as regulators with patient registries is quite extensive, of 116 centrally approved medicinal products in Europe between January 2007 and January 2011; 43 marketing approval dossiers contained one to six registries/registry-based studies.[1] Enrolment in these registries was, however, poor. [2,3] Existing registries were not fully exploited, with duplication of efforts when new registries are set up with the risk of scattered information. Regulators generally prefer patient (disease) registries over product registries, as these gather insights on clinical outcomes of conditions with different treatments, rather than on the outcomes of specific treatments, they allow comparisons, and are generally better integrated into health care systems.

In these existing disease registries, however, there was often a discrepancy between data collected and the data needed to answer regulatory questions. In addition, there were concerns with regards to data quality, (lack of) agreed standards/terminology and systematic quality control, missing data, representiveness of registry populations and many of these existing disease registries had funding problems that threatened sustained data collection.

Ultimately, these issues may then lead to pharmaceutical companies establishing their own product registries.

This was why in 2015 the EMA Patient Registry Initiative was launched and a cross committee Taskforce on Registries set up (https://www.ema.europa.eu /en/human-regulatory/post-authorisation/patient-registries). The main aim of the Initiative is to facilitate use of patient (disease) registries by introducing and supporting a systematic approach to their contribution to the benefit-risk evaluation of medicines. A key component of the Initiative is to promote a dialogue between regulators, companies and registry holders to understand barriers and opportunities of using disease registries.

The approach intends to mend the ‚broken' triangle, where regulators talk to industry and industry talks to registry holders, but there is no cross talk between regulators and the registry holder. The second key component is to clarify the difference between the concepts of a registry – in terms of the data collection – and the registry-based study.

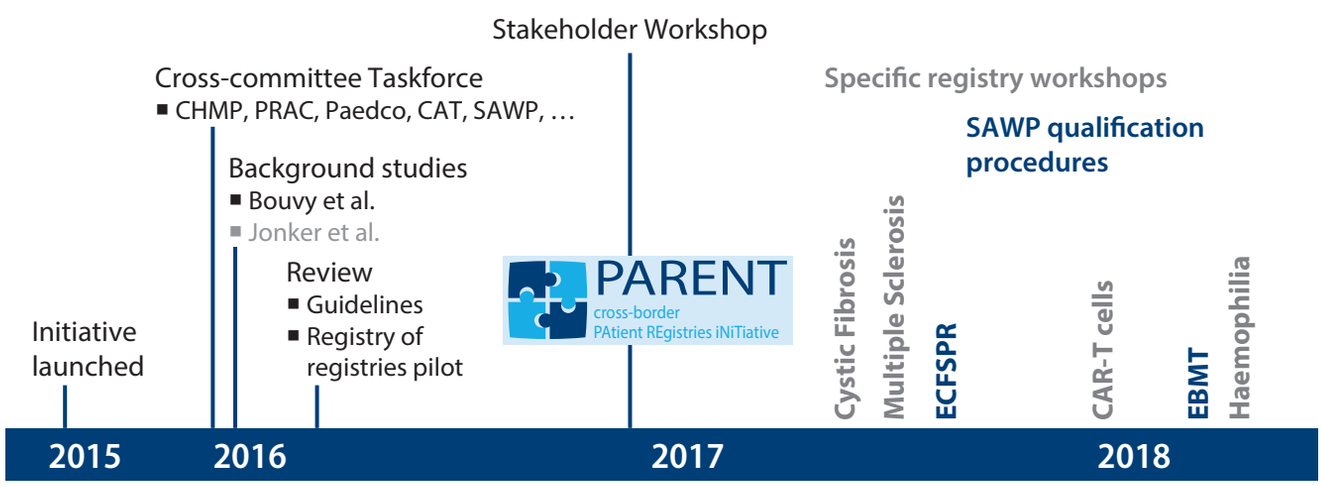
The Initiative embarked on a journey that started with an identification of registry guidance, and existing European registries that had been collected PARENT, Cross Border PAtient REgistries iNiTiative (PARENT), a Joint Action under the EU's Health Programme 2008-2013. (https://www.eunethta.eu/parent). [See Figure] In addition, the work highlighted above – publications by Jonker et al. [1,2] and Bouvy et al. [3] served as a baseline for regulatory experience with registries.

Subsequently, and the mainstay of the Taskforce's work is to facilitate interactions between industry, registry holders and regulators around disease areas with multiple new products in the pipeline and where there is an expectation RWD will be needed to address remaining uncertainties at time of approval. A number of workshops with a diversity of stakeholders were organised, i.e., around cystic fibrosis, multiple sclerosis, CAR-T cells, haemophilia and most recently for cancer therapies based on tumours' genetic and molecular features (November 2019). These workshops have a fixed format with a general introduction, laying out the regulator needs, (a) presentation(s) of the main available registry(ies) and break out sessions discussing three main topics; i.e., core data elements, data quality and governance. The paper ‚Patient Registries: An Underused Resource for Medicines Evaluation' by McGettigan et al. provides a good overview of the first four workshops.[4] It includes operational proposals for increasing the use of patient registries in regulatory assessments.

The Initiative also supports regulatory colleagues when in ongoing procedures issues with registries or registry-based studies are key to the decision-making process. Two

**Prof Peter Mol** *is a principal assessor at the Dutch Medicines Evaluation Board and a member (vice chair) of EMA's Scientific Advice Working Party. He is chair of the EMA Cross-Committee Task force on Registries. He is also an assistant professor at the University Medical Center Groningen. His research interest is in the area of regulatory science; from new tools to optimize regulatory decision-making (especially impact of personalised medicine and real world evidence), to improve knowledge transfer and with a specific interest in safety communication.*

**Milestones of the Patient Registries Initiative (Parent) since 2015**




Quelle: https://eunetha.eu/parent

important highlights in the Taksforce's ‚journey' are the qualification of two registries – ECFSPR (The European Cystic Fibrosis Society Patient Registry) and EBMT (The European Society for Blood & Marrow Transplantation Registry) – to support defined regulatory questions. The detailed reports, and specific regulatory ‚context of use' for these registries can be found on the EMA website (https://www.ema.europa.eu/en).

The Qualification of novel methodologies procedure, as the process leading to the qualification of the registries is called, is a voluntary regulatory pathway in which a new technology – such as Patient Reported Outcomes, biomarkers, and thus registries – can be acknowledged for certain use. These procedures involve an intensive interaction with the regulator, through the Scientific Advice Working Party, and a public consultation and results in the publication of the qualified technology – that is not linked to a specific product – on the website of the EMA (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development). It is important to realise though that even with such qualification of a registry, when a registry-based study is proposed the specific regulatory question will determine the data elements and quality assurance needed.

The research question determines the study design and preceeds the selection of the data. A study protocol should lay down the analysis plan and it is recommended to engage with scientific advice to plan and later to agree on a final protocol. Feltelius et al. also concluded in their survey of Swedish health care quality registries that close collaboration between registry holders and regulators could benefit regulatory utility by improving quality and usefulness of registry data [5].

In conclusion, data generated in clinical practice – including registry data – offers the possibility to address remai-

ning regulatory questions at approval. Disease registries are favoured over product registries, but it is key that design, data source and analysis are fit for purpose, and are agreed with the regulator. Case-by-case discussions will be needed to guide registry-based studies that deliver the answers needed. Acceptability of real world evidence is determined by the objective, i.e., safety and/or efficacy, and the role in regulatory decision-making. Higher standards are applied to studies and data sources (registries) – that are pivotal to decision-making rather than perform a supportive role.

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# Overview of registries in Germany

**Professor Jürgen Stausberg | Physician specialising in Medical Informatics and Medical Quality Management, member of the speaker team of the working group Registry of the German Network for Health Services Research**

*Registries are an established and well-defined method in healthcare research. They also make substantial contributions to clinical and population-based research. The basis for the operation of a registry is a structured protocol covering the registry's entire life cycle from the first considerations until its actual start. Any changes of the registry's tasks and research questions over time which are quite common for registries will also be documented in the registry protocol. Registries create new treatment knowledge on the basis of data from the clinical practice. For this purpose, registries use existing data that will be supplemented by additional data collections, e.g. on patient-reported endpoints. The lack of a national infrastructure for registries, however, results in insufficient data situation about ongoing projects and impedes the implementation of new projects.*

## 1 What is a registry?

Registries answer patient-oriented research questions in healthcare on the basis of a planned, systematic and carefully controlled data collection. Normally, no intervention takes place in a registry, neither preventively, diagnostically, therapeutically, nor palliatively. By contrast, registries observe the clinical practice in healthcare. Often, data to be collected for the registry are already available at the study centres; sometimes, new data is collected for a registry, e.g. on the quality of life or other patient-reported outcome measures (PROMS).

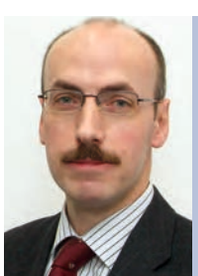
In most cases, registries monitor the observation units over a longer period with regard to treatment structures and processes. Registries are a key method for healthcare research.[1] Under the various pillars of health-related research[2,3,4] registries also make important contributions to clinical and population-related research (see figure 1). In clinical research, registries can be used e.g. for the evaluation of an additional benefit of pharmaceuticals or conduction of registry based randomised clinical trials (RRCT). In population-related research, epidemiological registries like cancer registries have been used for a long time.

In 2009, healthcare research and registries were still not mentioned in an overview of study types in medical research.[4] This might be attributable to the fact that when it comes to registries, different methodologies prevail competing for attention and funding priorities. It is therefore all the more important to clearly define the term „registry" without diminishing the significance of other approaches of observational quantitative research. In the first edition of their User's Guide for Registries,[5] the Agency for Healthcare Research and Quality (AHRQ) already defined registries as a „system" distinguishing them from registry data. Synonymous with „system", registries can also be referred

## Use of registries in the various pillars of health-related research


Source: Prof. Dr. Jürgen Stausberg

Figure 1: Registries are a key method in healthcare research. In health-related research, registries also contribute to clinical and population-related research.



*After his medical studies in Düsseldorf,* **Professor Jürgen Stausberg** *also qualified in Medical Informatics at the Städtische Krankenhaus Solingen and GSFForschungszentrum in Neuherberg. From 1994 to 2007, he was Head of the working group Medical Informatics at the University Hospital Essen. In 2001, he completed his postdoctoral lecturing qualification (habilitation) in Medical Informatics. From 2008 to 2014, he was professor for Medical Informatics at the Ludwig Maximilian University (LMU) in Munich. From 2015 to 2019, he was head of the division Documentation and Coding Quality at the Central Research Institute of Ambulatory Health Care.*

to as a project, method or study type. Unlike a RCT, variability and flexibility of registries may impair this perception. But only if registries are perceived as a type of study, an epistemological value can be expected that is different – in terms of the used methodology – from less controlled observational studies or the secondary use of existing – thus randomly created in terms of its use – data.

Thus, the level of understanding of registries has increased since the World Health Organization (WHO) defined the status quo in 1974.[6] If registries are considered a type of study, the term „registry study" is dispensable and misleading and the term „registry study" should therefore no longer be used. In its definition of 2010, the German Network for Health Services Research (DNVF e.V.) focuses on the aspect of documentation defining registries as an „as active as possible, standardised documentation of observation units on previously-defined research questions that can be expanded over time for which a precise relation to the target population can be reflected in a transparent

manner".[1] Figure 2 shows typical changes of a registry over time. It begins with the registry protocol in which the planning and design of a registry are stipulated on the basis of its objectives and tasks outlined by means of research questions and proposed analyses.

The funding programme of the Federal Ministry of Education and Research (BMBF) for the development of exemplary patient registries for healthcare research stipulated the creation of a registry protocol in a first funding period for concept development.[7] Hence, at the start of the registry with the inclusion of study subjects, a range of characteristics is available derived from research questions and analysis plan (metadata on t0).

In the further course, additional evaluations can be performed on the basis of existing data and/or new research questions within the scope of the defined tasks with subsequent changes of the characteristics for future data collection take place (metadata on t1). In terms of data protection regulations, this should still be possible on the basis of the informed consent set up with reference to objectives and tasks.

This will probably be different for the determination of further tasks or objectives, e.g. supplementation of a quality registry with tasks relating to pharmacovigilance. Expansion of an existing registry could also have an influence on the inclusion and exclusion criteria so that not only the characteristics but also the collective of a registry undergoes a transformation (metadata on t2).

These changes must be documented in the registry protocol so that the current status can be traced at any time. Studies can be fully integrated into the registry, e.g. a cohort study on the basis of an existing set of characteristics and the present collective (t3). By contrast, registry-based RCTs have a common data base of registry and RCT for all subjects included in the RRCT (metadata on t4).

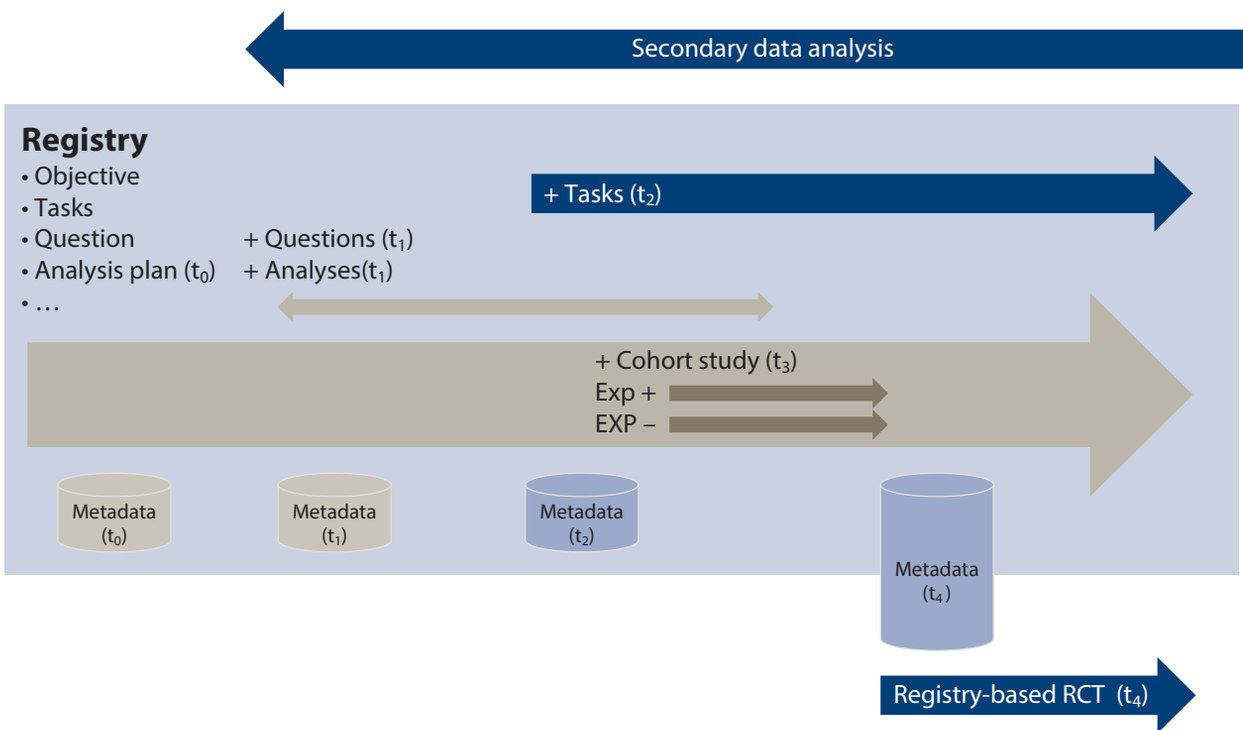
Secondary analyses of data can be performed at any time with the existing database as well as secondary analyses of RCTs or reimbursement procedures. However, the underlying study approach (RCT, registry, reimbursement documentation) can only be used indirectly for the new analysis. Population, endpoints, confounder, control of collection and recording, monitoring, etc. have not been customised to the new use. Like in all other uses of a registry outside the initial registry protocol, data protection and ethical matters must of course be evaluated. In order to promote a secondary use of data which is desirable for efficiency reasons in clinical practice, registries should incorporate the FAIR principles: Data should be findable, accessible, interoperable, and reusable.[8]

**2. „Real world data" in registries**

For registries, data from clinical practice are collected in order to gain insights about the day-to-day healthcare. RCTs are also conducted in healthcare institutions like hospitals and practices so that RCTs also use data from the clinical practice or at least data that have been collected and recorded in institutions and by the employees of these institutions.[9] During the approval of pharmaceuticals, this often applies from phase II and III. By contrast, the large cohorts in Germany like NAKO Health Review establish their own centres for the examination of subjects and collection of the required information so that data from the clinical practice do not have to be used in these cases.

Thus, to differentiate registries from RCTs, the term „real world data" is inappropriate. However, it must be distinguished between the collection of data from surveys or evaluations as well as the collection of such data within the scope of documentation. Registries are mainly based on data that have already been collected for other purposes and stored in the file. They can be transferred into the re-

## Potential changes of a registry over time




Source: Prof. Dr. Jürgen Stausberg

Figure 2: Hence, at the start of a registry with subjects, characteristics are available derived from research questions and analysis plan. New research questions can result in different ranges of characteristics.

gistry from the file or entered again for the registry. Control options of registries then comprise the specification of this second data collection.

Registries can control data collection, if these are explicitly collected for the purpose of the registry, e.g. recording of the quality of life in clinical practice, use of reference laboratories for the determination of laboratory parameters, or direct entry of experience and endpoints by the patients. Various control options are reflected by the measures of data management; comparison of collected data with the original data ensures that data of the second collection are equivalent to those that have initially been collected. If data are specifically collected and recorded for the registry, this is no longer a possible choice.

The term „real world data“ should not obscure that the participation in a registry or RCT has an influence on the behaviour of the participating institutions and thus on the treatment landscape in general. This is obvious in RCTs, as even reference groups of the actual intervention often receive a more conscientious care as it would be the case

without RCT. However, this also applies to registries to the extent that the procedures of collection, analysis and reporting are linked to treatment processes of the participating study centres. This is obvious in quality registries that explicitly draw comparisons between study centres, e.g. with the objective to implement quality measures. For this reason, statements from quality registries, e.g. on the frequency of adverse events, cannot be transferred directly to the overall population.

The use of data from the clinical practice is associated with several advantages and disadvantages. Refraining from collecting and recording new data saves costs and time. The clinical practice has already been represented. However, poor data quality from hospitals or practices might prove disadvantageous, as data collection cannot and data recording only partially be controlled. However, this is set against the much higher significance of data for the individual treatment of a patient as compared to their use in empirical studies. While faulty information in clinical practice can cause harm to a patient, it can be compensated via the case numbers in statistical analyses. Thus, it is questionable not to use data from clinical practice due to potential quality deficiencies.

To overcome this potential disadvantage, registries should be closely linked to the electronic file of the study sites (see figure 3 using the example of tumour documentation). Data would only be recorded once in the patient file and made available for all subsequent applications. Any further use of the data that have only been collected once will constitute a quality securing measure, as potential data quality issues are verified from different perspectives creating several correction loops. However, data from the file must be specified precisely enough for subsequent research projects by means of a systematic and structured basic or advanced documentation.

Coordination of metadata across applications, i.e. characteristics and value ranges of the respective data sets, is essential to ensure applicability. That this cannot be taken for granted, becomes obvious by the example of deviations in the basic characteristics – such as gender – between the requirements for clinical cancer registry and healthcare provision.[10] For this coordination, national services such as a metadata repository must be established.[11]

**3. Data quality and the efficacy-effectiveness gap**

The gap between findings on the efficacy of interventions in quasi-experimental studies like RCTs and findings on their actual efficacy in clinical practice, the so-called efficacy-effectiveness-gap, might be smaller than expected. At least, comparisons show a good correlation for many research questions regarding direction and extent of the effect.[12] Firstly, no additional evidence for the efficacy in clinical practice is usually required from a registry if a robust level of knowledge has been obtained from RCTs. Moreover, registries can also be used to address questions of the benefit assessment prior to interventions, if they fulfil the necessary requirements for such statements.

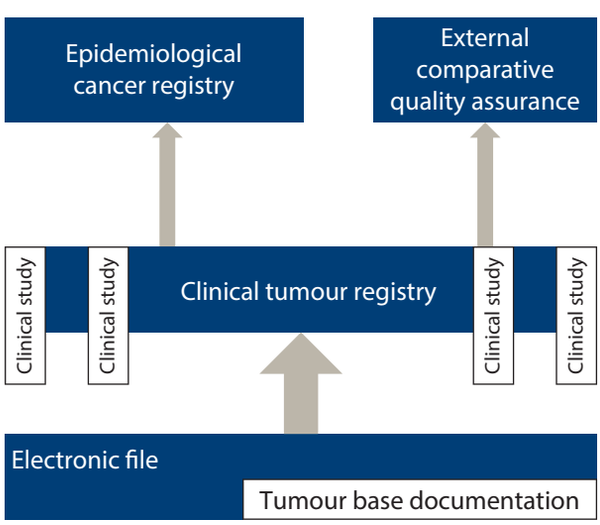
It needs to be clarified which criteria are used to select between an RCT and a registry. Thus, the hierarchy of evidence is also under discussion. So far, the study type – as structural feature – was supposed to determine the significance of findings. Traditionally, findings from RCTs were weighted higher than findings from registries. This determination will no longer be viable. The structural feature study type should rather be supplemented by an evaluation of the data quality that can be classified as a formal result of a study.

Such a hierarchy was already suggested for healthcare research,[13] with an increasing quality of study data, their potential contribution increases for the generation of hy-

potheses, to comparisons of healthcare programmes and treatment quality up to benefit assessment. In a first step, publications of study results should no longer only contain information on the study design, but also information about indicators of data quality. In a second step, composite measures on data quality could be developed to enable quantitative evaluation of the suitability of a study for certain research questions.

A summary of 51 indicators forms the basis for a networked medical research that should be used to aggregate a score.[14] A proposal for a core set of indicators for registries was published.[15] Against the background of the new legislation, these approaches must be further developed in order to replace the current evidence hierarchy by an evidence and quality hierarchy. Of course advantages of RCT – like randomisation and blinding – and advantages of registries – like the practical relevance – remain relevant, as these can only be reflected by means of characteristic of the quality of data to a limited extent.

**Use of treatment data for subsequent purposes as illustrated by the example of tumour documentation**




Quelle: Prof. Dr. Jürgen Stausberg

Figure 3: Data are only recorded in the patient file once and made available for all subsequent applications.

**4. Registries in Germany**

At present, there is no official body in and for Germany responsible for the registration of registries and provision of information about registries. In 2014, the DNVF already submitted a proposal for the contents of a registry for registries with the broad support of the member associations.[16] Despite many initiatives from the BMBF and Federal Ministry of Health (BMG) on registries, such an official body could not yet been established. Several initiatives for a registry for registries – also at international level – had little success:

- In the Cross-border Patient Registries Initiative PARENT – Patient Registries of Europe,[17] a set of registries was developed (http://parent-ror.eu/). Only 10 of the 214 entries are assigned to Germany (time of all queries: 16.10.2019). At present, this initiative seems to be at a standstill.
- The European Medicines Agency (EMA) has established a so-called „Resources Database" (see: http:// www.encepp.eu/encepp/resourcesDatabase.jsp). It is not clear to what extent resources are included there after marketing authorisation of a pharmaceutical. 40 of 140 data sets are included with German participation.
- The Registry of Patient Registries of the AHRQ was stopped due to a lack of resources (see: https://www.ahrq.gov/ropr/).

It is not feasible to include registries in compilations of clinical studies. An adequate description of registries can-

not be expected – like the DNVF has requested. Moreover, the registration of registries in these compilations is not subject to formal requirements and thus left to chance. However, such entries can be found in registries of clinical studies:

• Although registries can be registered in the German Clinical Trials Register (DRKS, see: https://www.drks.de), a search for this type of study is not possible. Thus, the free-text search using the word „registry" does not yield any usable result.

• In contrast, the US American ClinicalTrials.gov allows characterisation of an entry as „observational, patient registry study". At least 400 of 5,344 entries are assigned to Germany, while 249 of them are marked „active".

Only fragmentary systematic information is available on registries, e.g. on registries of medical research networks,[18] registries of professional associations or individual fields[19,20] or certain observation units.[21,22] Hence, the informed consent provides the most common basis for the operation of a registry. In light of the variable course of a registry with often long-term observation of the subjects, the design of the informed consent is paramount.

Within the scope of the registry's objectives and specific tasks, all possibilities to expand data collection and analysis should be taken into consideration and specified. To ensure that further changes can be obtained within the course of the registry, subjects should be contacted for an initial informed consent. The same applies for the alignment of collected data with original data. Unfortunately, all data protection recommendations relating to registries date back to the time before the European General Data Protection Regulation (GDPR) came into force.[23] Only few registries have their own legal basis. It was created for the epidemiological cancer registries with the request for national regulations with the Cancer Registry Act that was in force from 1995 to 1999. Across Germany, the establishment of clinical cancer registries is stipulated in Section 65c of the 5th German Social Codebook (SGB V), while implementation is regulated by the applicable laws at federal state level. Transplant and implants registry, however, have been implemented across Germany.

The transplant registry that is to be established in accordance with the Transplantation Act is mainly based on an informed consent. Both trust centre (https://www.tx-vst.de/) and registry office (https://transplantations-register.de/) are privately owned and operated. Notification of the implant registry is mandatory as well as communication to the affected patient. The implant registry has been implemented by federal institutions of the Department of the BMG. The registry office will be located at the German Institute for Medical Documentation and Information (DIMDI) and the trust centre at the Robert Koch Institute.

Besides the possibilities of an independent legal basis and informed consent, only some registries make use of the opening clause in Section 27 of the German Federal Data Protection Act (BDSG) on the processing of health-related data for scientific purposes without the consent of the data subjects. Moreover, the rights of data subjects regarding access, rectification, and deletion as specified in the GDPR are restricted. It remains to be seen whether and to what extent registries can claim the conditions for the use of opening clause mentioned in the BDSG.

**5. Observation units of a registry**

It may seem self-evident that the discussed registries observe human beings and not animals or other objects as study subjects. However, this does no longer apply for the assumption that these are patients, i.e. diseased persons who are in contact with healthcare institutions. In fact, healthy persons are also recruited, e.g. as a living donor for

transplants, recipient of a preventive service such as a vaccination, or relative with or without the risk for a genetically-related diseases. Therefore, it is appropriate to abstract human beings as objects in the differentiation of registries by observation units.

• Registries itself and the inclusion of persons are often defined by diseases.[24] These may be common diseases like diabetes mellitus or dementia, but also rare diseases like cystic fibrosis (mucoviscidosis). Symptom or harm-related registries must also be assigned to disease-registries, e.g. registries on fever or paraplegia. In case of chronic diseases, persons are included once and then followed-up for a lifetime over the course of their disease, where appropriate. In case of acute and recurrent diseases, a decision must be taken as to whether each incidence is considered independent and the diseased person is thus included several times or whether multiple incidents over time are assigned to a person who has been included once.

• In case of surgical or interventional treatments, the respective procedure is often of primary importance.[25] If the procedure is performed for different indications – like in case of minimally-invasive surgical procedures – the registry comprises heterogeneous diseases. This fact might necessitate the definition of specific modules with different metadata for various indications of a procedure. Also in this case, a person can be recruited several times, if the procedure resulting in the inclusion can be performed several times for different indications.

• In medical device registries, not the procedure for the application of a product is of primary importance, e.g. implantation of a hip endoprosthesis, but the product itself.[26] Even though an application of a medical device always seems to be connected with a procedure performed at a healthcare institution, this is no longer the case when looking at apps. Thus, procedural and medical device registries overlap. However, both perspectives retain their individual significance. In medical device registries, multiple inclusions of a person are also possible, both related to the same produce type and across product types. These registries often serve for quality assurance purposes.

• Pharmaceuticals present another type of observation unit. Drug registries are associated with a specific indication, e.g. rheumatology.[20] Thus, drug registries combine aspects of all three mentioned types. Registries for the monitoring of the drug safety after approval are a special case. If one indication is missing or application restrictions require concentration on only few institutions, their implementation might be difficult. The identification of rare adverse events requires almost full inclusion of all prescriptions of the pharmaceutical. This necessitates a broad diversification of the registry across many institutions that might not really be affected by adverse events. In this situation, it is useful to use alternative routine data of the institutions as a basis for surveillance.

**6. Objectives of registries**

Registries observe the clinical practice of healthcare. They are therefore able to examine treatment structures and processes. This mainly applies for disease registries (see above) with event-related collection of relevant features like interventions or complications. Event-related collection requires concurrent documentation that is not associated with predefined follow-up times, but each incidence is recorded.

For this reason, defined follow-ups e.g. on the quality of life or aftercare are often combined with an event-related collection. For any events occurring during the course of the disease and endpoints, registries are a suitable method for the determination of prevalence and incidence. Even in disease registries, the frequency of the diseases itself can

only be estimated under special conditions. Ideally, this is includes completeness of the registration of affected persons like with epidemiological cancer registries or at least a clear relationship between evaluation collective and target population. Moreover, reference information must be available establishing a relation to the general population. With data on disease frequencies, distribution of disease stages as well as indications and frequency of interventions, registries can determine the treatment demand and support treatment planning.

Quality registries observe the relationship between structures and processes of treatment and patient outcomes. They compare institutions, sectors, or alternative treatment strategies. With adverse events, the results can comprise aspects of patient safety, PROMs or medically-relevant endpoints. Evaluation of the efficacy of certain interventions in the clinical routine serves to close the efficacy effectiveness gap. Within the scope of health economic objectives, registries can be used to determine utilisation patterns of insured persons and patients as well as service structure of the institutions. Especially for these applications, a representative selection of the study centres of the evaluated healthcare section is important.

Supporting clinical research with registries has a long tradition. New hypotheses are derived from registry findings that are subsequently evaluated by means of a clinical study. Registries can be used for the estimation of case numbers and recruiting potential participants for clinical studies. In RRCTs, registries and RCTs are combined in the database and at study subject level. However, these study subjects are subject to the quasi-experimental situation of the RTC and are thus no longer fully equivalent to the remaining registry collective without limitation. By appropriately combining an RRCT and a registry, efficacy and efficiency can be evaluated simultaneously. For any conclusions on benefit assessment, the best possible statistical approach is required to compensate for the missing randomisation, e.g. propensity scores. Disadvantages of registries regarding their internal validity must be weighed against their advantages regarding external validity.

**7. Outlook and future requirements**

At present, we experience a great euphoria regarding the use of registries. New registries are established on a legal basis across Germany, funding programme are set up for registries, and the legislator accepts findings from registries to be used as a basis for new objectives, such as benefit assessment. However, in this current state of euphoria, the status quo of the methodology of registries must not be forgotten. Registries present a systematically planned and strictly controlled study type of health-related research; by no means must registries be reduced to a mere set of data that is evaluated within the scope of secondary analyses. The working group Registry of the DNVF has therefore elaborated an update of Memorandum Registry for Health Services Research in which the methodology of registries are clearly and practicably explained.[27]

In Germany, a national infrastructure is currently missing to support research activities using registries. First of all, it should be mentioned that there is no registry for registries. This gap leads to redundant developments, as nobody knows which registries have been established on which topic in Germany. There is also no clearly defined source of information for institutions, patients, and the interested public. A metadata repository provides the basis for the harmonisation, alignment and standardisation of contents of health-related datasets. With the objective of a single collection and multiple uses of data as shown in figure 2, the metadata repository would not only comprise treatment research, but also treatment.

At present, registries become increasingly interconnected and integrate data from other datasets – besides their own active collection. One essential prerequisite for this is the clear, uniform and lifelong labelling of patients, that can be used for record linkage even in case of pseudonymised data. In a second step, such a labelling is also feasible at the level of individual information objects. At least for the endpoint death, a mortality registry should be established as a central service providing information on this endpoint, independent of individual enquiries to registrations offices and other institutions.

With an increasing number of registries, a competition for study centres and subjects will develop which will have to be supported from the IT perspective. In addition to the treatment-supporting IT systems, individual e.g. web-based collections tools of hospitals and practices would then no longer be feasible. Local IT systems are required combining documentation requirements of registries in one uniform interface in a transparent manner, if the required data are not already available in the electronical file. In future, the patient and citizen will no longer be regarded as an observation unit in registries, but plays an important role as an individual study centre.

Clearly defined financing means are required to ensure a sustainable operation of registries. To ensure funding, both options including statutory and private health insurance companies should be taken into consideration and involvement of pharmaceutical companies or medical device manufacturers, e.g. by means of a pool model that ensures the required scientific independence.

For any queries regarding the further development of healthcare research with registries you can contact the working group Registry of the DNVF (see: https://www.netzwerk-versorgungsforschung.de/index.php?page=ag-register).

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# Hierarchy of evidence and registry data: The IQWiG's perspective

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*With the Act for Greater Safety in the Pharmaceutical Supply System (GSAV), the legislator has authorised the Federal Joint Committee (G-BA) to impose the obligation on pharmaceutical companies to generate additional data within the scope of post-market data collection in certain situations. Certain statements in the law and the explanatory memorandum suggest that these are not supposed to be randomised studies, while registry studies could play a key role. In order to outline the significance of registry data in the sense of a „hierarchy of evidence", the (research)question to be addressed must first be defined. Fair comparative conditions must be established to be able to address questions about the effects of certain medical interventions. Every study design that can ensure fair comparative conditions will be at the top of the hierarchy of evidence for benefit assessments. It is important to ensure that data reflects the relevant PICO elements (Patient, Intervention, Comparator, Outcome) in the required quality. Scientific requirements regarding robustness and transparency demand a study protocol, an analysis plan, a publication plan as well as a registration. It is not acceptable to tolerate a lower data quality in non-randomised studies than in high-quality clinical studies with common regulatory requirements.*

## Background

With the Act for Greater Safety in the Pharmaceutical Supply System (GSAV), the legislator has authorised the Federal Joint Committee (G-BA) to impose the obligation on pharmaceutical companies to generate additional data within the scope of post-market data collection in certain situations in addition to data they already submitted within the scope of the original assessment.[1] These situations comprise marketing authorisations (MA) for pharmaceuticals on the basis of provisions for rare diseases (orphan drugs), conditional approval, and MA under exceptional circumstances. The objective of this statutory provision is primarily to close evidence gaps thus enabling the G-BA to quantify the extent of the determined additional benefit.

Strangely enough, the legislator has more or less explicitly excluded the so-called gold standard for benefit assessments of medical interventions, i.e. randomised controlled trials (RCTs). At least, the following sentence of the statutory provision allows such an interpretation: „The Federal Joint Committee can also request indication-related data collection without randomisation".[1] Theoretically, this sentence could also be interpreted differently, but the discussion[2] and explanatory memorandum of the Federal Ministry of Health (BMG) do not indicate that. The explanatory memorandum[3] states: „As data are collected within the scope of post-market data collection, there are no restrictions for prescribing physicians regarding the supply of pharmaceuticals (e.g. no randomisation or study specifications)". And further: „Such accompanying data collections can involve observational studies, case-control studies, or registry studies. (…) Thus, randomised blinded-assessor clinical studies are not included."

Moreover, the BMG lately expressed its reluctant appreciation of RCTs also in connection with the German Act

Establishing a Medical Implants Registry (Implant Registry Establishment Law, EIRD) and on further changes of the 5th German Social Codebook (SGB V) and the Act to Improve Healthcare Provision through Digitalisation and Innovation (Digital Healthcare Act – DVG).[4,5] The future vote behaviour of the G-BA on the one hand and potential (non)objections of the corresponding G-BA decisions by the BMG on the other side will tell.

**„Hierarchy of evidence" and research questions**

Assuming that the GSAV does in fact not consider RCTs, data collections within the scope of registries will play a key role. It should, however be defined in the next step how we define a registry. For the present article, the following rough definition shall be sufficient: A registry consists of the infrastructure for the structured and standardised data collection, data collection itself, as well as data storage.

In order to outline the significance of registry data in the sense of a „hierarchy of evidence", i.e. ranking from reliable to very unreliable, the (research)question to be addressed must first be defined e.g. by means of data from a registry or from other sources. Potential research questions are outlined in box 1.

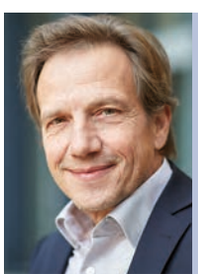
Thus it becomes immediately apparent that certain data sources are more suitable than others to answer the various questions. For example, in order to determine the therapeutic goals from the patients' perspective, focus groups can be a valuable instrument, while RCTs are certainly unsuitable. If, however, the additional benefit of a pharmaceutical shall be evaluated, case reports and expert opinions should normally not matter, whereas comparative studies are primarily required. As mentioned above, RCT is considered the „gold standard" and is ranked very high in the evidence hierarchy. In this context, it is irrelevant that with RCTs not all relevant questions might be addressed (e.g. addressing very rare adverse events). Thus, many concerns related to RCTs prove to be unjustified upon a closer look.[6]

**Registry studies**

What about the ranking of registries in the „hierarchy of evidence" in connection with the early benefit assessment of pharmaceuticals for which the question of an additional benefit as compared to one (or several) appropriate comparative treatment(s) shall be addressed? Firstly, it should be recognized that this is not a matter of registries, but of registry studies, i.e. the scientific collection, evaluation and analysis of data (from a registry).

This means that a registry study needs to have study protocol, an analysis plan, a publication plan, as well as a registration in order to meet scientific requirements regarding robustness and transparency. By the way, the term „registry study" does not necessarily imply a non-randomised study, because within registries patients can also be recruited for a registry-based RCT.[7,8]

Besides these general requirements regarding the scientific quality of studies, there are numerous papers outlining



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## Potential research questions

- What is the stage distribution at the time of the initial diagnosis of disease X?
- What are the therapeutic goals for patients with disease X in stage Y?
- Which symptoms and adverse events bother patients with disease X most? Does this change within the course of the disease?
- How often is therapy A used in patients with disease X?
- Which therapy sequences are used in patients with disease X? And can certain determinants be outlined?
- Do prognoses for disease X differ between the individual federal states of Germany? Does the treatment in centres make a difference?
- Do prognoses for disease X differ between therapy A and therapy B?
- Does therapy A have a greater benefit as compared to therapy B in patients with disease X in stage Y?

Quelle: PD Dr. Stefan Lange

Box 1: In order to outline the significance of registry data in the sense of a „hierarchy of evidence", a research question that shall be addressed with the registry data must first be defined.

(also) more specific requirements for the infrastructure (of a registry) itself and for data collection. Alongside many other aspects, sampling (e.g. completeness, representativeness, integrity) and data quality (data correctness) are crucial. This involves such aspects as ensuring data integrity (availability of log files), source data verification, monitoring, plausibility checks, automated verifications, queries, use of standard classifications and terminologies, as well as the possibility of performing audits. Examples of these documents are illustrated in box 2.

The fact that these requirements are definitely not met by all registries, becomes obvious by the example of two current papers from the surroundings of the EUnetHTA and the EMA. It seems to be of particular concern here that in particular requirements regarding data quality are often not met by registries.[13,14] So it is quite unfair that their – supposedly – being too expensive and complex is always considered (one) disadvantage of clinical studies. For it is especially the high data quality resulting from regulatory requirements that makes clinical studies expensive and complex. Specific requirements that need to be considered also relate to the planning and conduction of studies, e.g. clinical studies (Good Clinical Practice [GCP][15]), epidemiological studies (Good Epidemiological Practice [GEP][16], especially pharmacoepidemiology: The ENCePP Code of Conduct of the EMA[17]), or qualitative studies (GRADE CERQual[18]). The Cochrane Collaboration has developed a tool for the evaluation of the risk of bias of randomised and another one for non-randomised intervention studies (RoB tool19, ROBINS-I20).

**Comparison**

Although this might seem trivial, it should be noted that the question of a potential (additional) benefit always requires a comparison. One statement reads as follows: „The administration of pharmaceutical A yields a success rate of

## Papers outlining specific requirements for regist

- German Network for Health Services Research (Deutsches Netzwerk Versorgungsforschung e. V. (DNVF e. V.). Memorandum Registry for Health Services Research [9]. Under revision.
- European Medicines Agency (EMA). Discussion Paper: Use of patient registries for regulatory purposes [10] In this paper, the important differences between registry and registry study are explained.
- Agency for Healthcare Research and Quality (AHRQ). Registries for evaluating patient outcomes [11].
- European Network for Health Technology Assessment (EUnetHTA). Vision paper on the sustainable availability oft he proposed Registry Evaluation and Quality Standards Tool (REQueST) [12].

Source: PD Dr. Stefan Lange

Box 2: Specific requirements as outlined in these documents relate to the infrastructure of a registry and data collection – for example aspects of sampling and data quality.

30 percent in patients with disease X" does only make sense, if the success rate without this pharmaceutical or with an alternative has previously been determined. This might be implicit in very rare deterministic situations, but it must be made explicit as a general rule.

However, this involves a principal impossibility: It cannot be determined in one person what would have happened if this particular person had received therapy B instead of therapy A, i.e. A counterfactual intervention.21 However, it should be neglected that there are rare extraordinary circumstances that will come close to such a counterfactual approach under certain assumptions, e.g. the use of different interventions in paired organs.

This impossibility results in the necessity of comparing groups who underwent different interventions. There are exceptions to this, too, i.e. serial use of different interventions in one person (cross-over studies) that do, however, practically play no role whatsoever for the benefit assessment and also require further assumptions. Such a comparison of groups only allows for reasonable interpretations, if the starting conditions are „fair", i.e. comparable.

Moreover, from the beginning of the study until the determination of relevant outcomes, the conditions for the groups, except for the interventions in question, must not be systematically different. Every study design that can ensure this will be at the top of the hierarchy of evidence for benefit assessments. It is obvious that such „fairness" can be most effectively achieved with a randomised group allocation.

**Target trial and other approaches**

In their quite recent publication, Hernán and Robin suggest to emulate a target trial using „big data" that comes close to the ideal of a high-quality clinical study.[22] For this idea, the underlying data source is primarily irrelevant, i.e. whether data are in fact „big data" in the proper sense (e.g. routine data of health insurances) or data from a non-randomised registry study. However, it must be ensured that data reflects the relevant PICO elements (Patient, Intervention, Comparator, Outcome) in the required quality to be suitable to address questions of the (additional)benefit assessment. E.g. approval-compliant application but

possibly also important biological (such as genetic) markers must be taken into consideration. Moreover, all relevant endpoints (mortality, morbidity [symptoms, adverse events], health-related quality of life) must be determined using valid instruments. Another result of the need for a comparison is that disease-registries are more suitable to address questions of benefit assessment than product-registries. This is due to the fact that in product-registries, a parallel comparison can only be realised across different registries which in turn requires that 1. there is another registry in which 2. the necessary data are collected in a similar way.

In very rare exceptional cases, it might be possible to make a „historic" comparison, i.e. compare the results of patients who are currently treated with pharmaceutical A with patients who had previously received another, possibly only supportive therapy. However, such a comparison requires considerable prior knowledge about the course in terms of patient-relevant endpoints from the past so that a certain determinism can be assumed.

Secondly, the expected difference must be that big („dramatic") so that it can no longer be attributable to bias and renders a parallel study obsolete.[23] Moreover, both prerequisites should be formalised. This means that all information on the „historical" course must be systematically collected and must not be presented selectively. And the „expectation" (of a dramatic difference) must be explicitly included into the statistical (nought)hypothesis formulation (or an equivalent thereof).[24]

In very rare diseases, another approach can be interesting, i.e. supplementing the results of the RCTs with (very) small case numbers by those of non-randomised studies (e.g. from register studies meeting the above mentioned requirements).[25] Ultimately, this results in something similar like raising the statistical margin of error above the normal value of (2-sided) five percent in RCTs in very rare diseases[26], yet on an informed basis.

**Conclusion**

Data from registry studies can be ranked very high or significantly further below in the evidence hierarchy. This depends on the research question and the quality of the registry. Fair comparative conditions must be set up to be able to address questions about the effects of certain medical interventions. Every study design that can ensure fair comparative conditions will be at the top of the hierarchy of evidence for benefit assessments. It is important to ensure that data reflects the relevant PICO elements in the required quality both in RCTs as in non-randomised registry studies.

It would not be acceptable to tolerate a lower data quality (data integrity and correctness) in non-randomised studies than in RCTs with common regulatory requirements. A registry study, regardless whether it is randomised or not, (also) needs a study protocol, an analysis plan, and a publication plan. Registry studies should (also) be subject to a registration obligation.

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# Additional benefit of registry data – for early benefit assessment

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*In order to ensure a fast market access and availability of all types of pharmaceuticals in future – including those with limited evidence at the time of approval – the data situation in certain cases must be further improved. The identification of the cases in which supplemental data generation is feasible and the specification of the requirements as to how these data are collected and evaluated will present a challenge for the G-BA. Among the available study designs, registry studies are one option that might be suitable to generate the necessary evidence for benefit assessment. Before the conduction of a registry study is imposed as a condition, it should always be verified whether the body of evidence can be improved by adapting the study design in the course of clinical development programs. Do data collected within the scope of post-market surveillance have the required quality and do they answer the predefined research question, does the systematic integration of these additional data together with other available evidence provide an extended decision base for the benefit assessment with subsequent price negotiation.*

## Background

With the Act for Greater Safety in the Pharmaceutical Supply System (GSAV) that entered into force in 2019, the legislator equipped the Federal Joint Committee (G-BA) with a tool to impose binding regulatory requirements relating to data collection for the purpose of benefit assessment. This option applies to pharmaceuticals with orphan drug approval, conditional marketing authorisation, or marketing authorisation under exceptional circumstances.

With the new Paragraph 3b in Section 35a SGB V, the G-BA can – in case of insufficient data – impose an obligation on the pharmaceutical company to perform or have performed post-market surveillance for the purpose of benefit assessment. For this purpose, the G-BA must specify details such as duration, type, scope, analysis, format, methodology, as well as patient-relevant endpoints. Indeed, the competence to prescribe the pharmaceutical at the expense of the statutory health insurance can be restricted to care providers participating in the requested post-market surveillance.

This means that besides the decision pursuant to Section 35a SGB V on the benefit assessment of a pharmaceutical further decisions must be taken as to whether and in particular in which form and according to what specifications post-market surveillance shall be performed and whether prescription of the respective pharmaceutical shall be restricted to participating service providers.

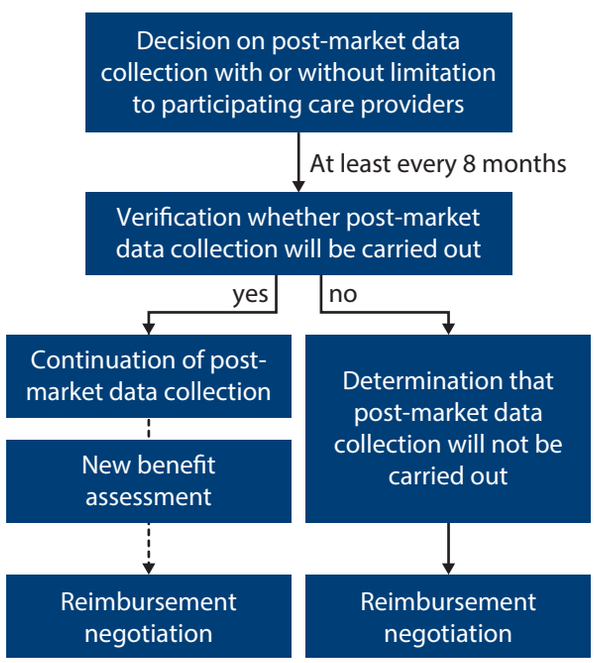
Moreover, the G-BA must review at least every 18 months whether the pharmaceutical company fulfils its obligation of post-market surveillance; otherwise, the National Association of Statutory Health Insurance Funds (GKV Spitzenverband) can request renegotiation of the reimbursement amount according to Section 130b Paragraph 3. For this purpose, the G-BA must determine that data col-

lection either is or cannot be performed or will not provide sufficient evidence for the reevaluation of the additional benefit for any other reason. The G-BA must define transparent procedures and decision-making criteria to define circumstances in which it can no longer be expected that the requested data collection will be performed or has a realistic chance of success (see figure 1).

After completion of the post-market surveillance, another benefit assessment is performed according to Section 35a SGB V during which the new data will be considered in combination with the known data and further data on this pharmaceutical (where appropriate); thereafter, the reimbursement amount will be renegotiated. If the additional benefit could not be quantified during the initial evaluation of a pharmaceutical with orphan drug approval, as the additional benefit could not be quantified on the basis of the scientific database, and can still not be quantified after consideration of the results of the post-market surveillance, a reimbursement amount shall be agreed upon that reasonably results in lower annual treatment costs as compared to the previously agreed reimbursement amount.

Thus, an increased reliability of the results alone does not represent an adequate result. This demonstrates that the requested data collection must be suitable as such to yield sufficiently reliable results. Moreover, sufficiently large effects must be expectable to allow for a quantification of the additional benefit. Supplementing already frag-

## Process flow for decisions on post-market data collection




Source: own research

Figure 1: A decision for post-market surveillance is preceded by several process steps in the Federal Joint Committee.

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mentary data from weak evidence with additional very unreliable data is not very useful for the determination of the extent of the additional benefit and can even complicate and impair the decision-making process.

Even if it might be interesting to impose high-quality post-market surveillance as a condition for orphan drugs with a quantifiable additional benefit, e.g. if quantification is based on an endpoint that is less relevant for the indication, this provision might not be suitable for this purpose. This is understandable, as is it not reasonable to readdress research questions that have already been answered with more reliable evidence in further studies or only marginally substantiate certain (unreliable) results with further evidence.

Moreover, post-market surveillance is not a general method to subsequently correct deficiencies in case of unsatisfactory benefit assessments and cannot serve as a fundamental review of an already quantified additional use, but represents the basis for renegotiations of the reimbursement amount in carefully selected cases.

However, as collected data are processed in such a way that they can be used for a transparent evaluation procedure and are thus not only available to the stakeholders of the reimbursement negotiations, i.e. negotiation specialists and lawyers, but also to service providers in clinical practice and patients, it would be regrettable to reduce this instrument to a mere pricing tool against the background of the effort that needs to be invested in the planning and conduction of data collection – on the part of all service providers involved in the collection of the data, the pharmaceutical company, and the G-BA.

In my opinion, it must also serve to address patient-relevant questions, especially relating to the long-term effects, which have remained unanswered during benefit assessment (see figure 2).

**Chances and challenges in the implementation of Section 35a Paragraph 3 b SGB V**

As simple and promising as this provision might seem at first glance, the more complex it turns out to be in the details of the design and implementation. Firstly, it would be desirable that a request for post-market surveillance can be put into practice in the German care landscape directly after market entry of a pharmaceutical, i.e. literally „application accompanying".

In this way, the requested data can be collected from day 1 of prescribability, especially in very rare diseases or pharmaceuticals with single application. Moreover, it would already be transparent at the launch of a pharmaceutical in which type of data collection service providers shall participate, provided that only participating physicians and hospitals can prescribe the pharmaceutical.

Especially this limitation of the circle of prescribers can help to ensure that comprehensive data are collected and almost all patients receiving this pharmaceutical are included into the data collection. It should be emphasised that the patients' general access to this therapy is not limited and there are no quality requirements for the selection of the circle of prescribers, except for the obligation to collaborate, unless a provision according to Section 136a Paragraph 5 applies (for advanced therapy medicinal product, ATMPs).

On the other hand, the question arises whether a request for post-market surveillance is possible at the time of market launch both from a professional and a legal point of view. As the G-BA must must specify the details for the implementation of the post-market surveillance, it is essential to examine the evidence in detail. However, this evidence is only explored at a sufficient level of detail and considered within the scope of the benefit assessment. It might thus appear to be necessary to wait until the benefit

## Overview of the content of the Law for more Safety in Drug Supply (GSAV)

**Section 35 a para. 3 b SGB V**

- By the pharmaceutical company
- For the purpose of benefit assessment for
  - conditional approval
  - market authorisation under exceptional circumstances
  - orphan drugs
- Potential restriction to care providers participating in the requested post-market data collection
- Specifications of the G-BA in terms of design, duration, methodology, endpoints, etc.
- Ongoing and planned data collection must be considered
- Also indication-related data collection without randomisation
- BfArM and PEI must be involved prior to the adoption of a measure
- To review [..] reviews at least every months

**Section 130 b para. 3**

- After expiration of the deadline for data collection
  - new benefit assessment
  - If no quantification is possible: Lower reimbursement amount than the previously agreed reimbursement amount
- Before expiration of the deadline for data collection
  - Renegotiation of the reimbursement amount, if the G-BA determines that no, that data collection will be performed

Source: own research

Figure 2: It would be useful, if data that have been collection within the scope of post-market surveillance also served to answer patient-relevant questions which have remained unanswered during benefit assessment.

assessment has been completed. Moreover, for a timely implementation of data collection existing data collection structures are required, e.g. an existing registry.

Upon the implementation of such an infrastructure, organisation of data collection and the development of e.g. study protocols and analysis plans require time and a solid, meticulous planning. All this might not yet be available at the time of market launch. Besides that, the possibility to request post-market surveillance is bound to certain approval formats and the status of approval, e.g. orphan drug status, is sometimes only finally determined at a late stage in the approval process.

Apart from that, it can often be anticipated early in the clinical development of a product that certain milestones

will not be available for benefit assessment, e.g. overall survival data, patient-relevant morbidity, quality of life parameters, or data on adverse events. Consultations with regulatory authorities and pharmaceutical companies must take place at an early stage in order to identify the gap – using a structured gap analysis – between expectations regarding benefit assessment and approval evidence and the evidence that will probably be available at the time of benefit assessment.

Early consultations could also reveal that parallel to the clinical studies e.g. registries have already been established and implemented collecting data on the natural course or on patients undergoing standard therapy. This can counteract distortions caused by the fact that after market entry almost exclusively data on the new pharmaceutical are collected and data on untreated patients or patients treated with alternative therapies, respectively, can no longer be collected as the new pharmaceutical is now available.

The legislator has also explicitly specified, that consultations of pharmaceutical companies involving regulatory authorities can include questions on post-market surveillance and that the competent higher federal authorities must be involved, before the decision on the request for post-market surveillance is taken so that the accompanying data collection can be coordinated with approval-related requirements and regulatory requirements.

These regulatory requirements can vary significantly depending on the type of approval: e.g. in case of market authorisation under exceptional circumstances, regulatory authorities can basically not expect any further evidence according to the procedure of Article 14 Paragraph 7 or Paragraph 8 of Regulation (EC) No. 726/2004. In case of so-called conditional marketing authorisation, the commission usually imposes certain regulatory requirements or conditions on the pharmaceutical company that must be fulfilled within a specified time limit in order to receive approval. For example, the marketing authorization holder (MA holder) must initiate or complete certain studies to demonstrate a positive benefit risk ratio and answer open questions regarding quality, safety, and efficacy of the pharmaceutical.

The approval of pharmaceuticals for the treatment of a rare disease can be associated with further regulatory requirements in certain cases even without conditional marketing authorisation, however, without the consequence of a threatening withdrawal of the approval. According to the regulatory authorities – pharmaceuticals that are urgently required for the treatment of patients and will thus receive a specific regulatory approval or marketing authorisation, respectively, even if comprehensive clinical data are not yet available for the evaluation of their efficacy or only little evidence is available, e.g. due to the rareness of the disease.

Due to the limited therapy options for rare diseases, rapid market availability of these pharmaceuticals is considered as an advantage outweighing the risk of limited clinical data. But exactly these limited clinical data or rather the information that is not available reinforces the need to keep an eye on and later address these uncertainties.

To get an overview of the possibilities and instruments for data generation, the IQWiG was commissioned with the scientific elaboration of concepts for the generation and analysis of treatment-related data for the purpose of benefit assessment of pharmaceuticals by decision of 2 May 2019 according to Section 35a SGB V. This concept will provide the basis for consultations within the G-BA, which type of data collection can be suitable in which cases and what can be expected from data collection. In the explanatory memorandum on the GSAV, observational studies and

case-control studies are mentioned, while randomised blinded clinical studies are explicitly excluded as an option to impose conditions, as data collection should be observational, i.e. accompanying the use in clinical practice.

Even if this approach is understandable from the legislator's perspective – provided that an additional benefit must be quantified – the difficulty here is to derive high-quality data for benefit assessment. Our principal challenge will be not to have unnecessary data collected that might even contribute to an increased level of uncertainty and confusion during decision making. More data do not necessarily allow for clearer interpretations and more straightforward decisions. The explanatory memorandum and the discussion in the G-BA show that a focus is particularly on registry studies.

Indication registries are emphasised, as they provided the possibility to also generate comparative data – where applicable – as compared to an adequate comparative treatment, even if an appropriate comparative treatment is usually not determined in case of orphan drugs. In some cases, existing registries can also be used.

However, experiences of regulatory authorities with requested registries show that the imposed conditions can only be implemented with major difficulties. According to a Bouvy et al. (2017), the Committee for Medicinal Products for Human Use of the EMA (CHMP) requested 31 registries for 30 products in the period between 2005 and 2013, most of them in connection with risk management plans. Most frequently in percentage terms, registries for pharmaceuticals with conditional marketing authorisation were requested.

Only 24 registries could actually include patients, but most of them were product registries. The most reported problems with registries were a delayed start and small number of included patients. Especially with regard to the inclusion of patients into registries, the new provision in the GSAV could be exemplary in clinical practice, to support coordination of requirements for approval and HTA by national provision thus making them practicable.

The coordination of post-market surveillance with a renegotiation of the reimbursement amount alone is a consequence that shall encourage pharmaceutical companies to work intensively on data collection. As regulatory requirements are imposed on pharmaceutical companies, regulatory authorities and G-BA are faced with the problem, that the establishment of indication-specific registries cannot be imposed on individual pharmaceutical companies.

If indication-specific registries already exist, it is up to the pharmaceutical company and registry operator to specify the details contractually. The authorities' exertion of influence as to which registry the company uses to address its research question is thus limited.

However, pharmaceutical companies also don't have all options to implement their requirements in registries. That poses the risk that again product-specific registries will be established. In individual cases, product-specific registries are suitable to answer isolated individual research questions, e.g. on side effects, but for the evaluation of the additional benefit the overall endpoints are essential, i.e. comparative evaluation of the benefit in patient-relevant endpoints in combination with adverse events. An imbalanced data collection after market entry with a shift towards the pharmaceutical under evaluation might not be completely avoidable even with indication-registries, but should not be encouraged per se.

**Regulatory requirements of approval and benefit assessment procedures**

Even before the GSAV came into force, decisions for early benefit assessment had time limitations to enable inclusi-

on of study data that are expected from ongoing phase II studies, new study dates from registries that have been imposed as a condition by regulatory authorities and further safety assessments or data from registries imposed as a condition into a new benefit assessment. At present, decisions on approximately 40 procedures have a time limitation, and the results of these conditions imposed by regulatory authorities shall be integrated into the new benefit assessment.

Currently temporary decisions also comprise substances that have neither received an approval as orphan drug nor a conditional marketing authorisation or marketing authorisation under exceptional circumstances or orphan drug decisions with a quantifiable additional benefit. For these procedures, it is still possible to request data within the scope of a time-limitation. For orphan drugs or atypically approved pharmaceuticals, conditions do not necessarily have to be imposed in form of post-market surveillance, but also with a time limit.

In some temporary decisions, data from registry studies were explicitly requested, including asfotase alfa, sebelipase alfa, idebenone, cerliponase alfa, or afamelanotide.

The situation of asfotase alfa will be set out in details: The approval of asfotase alfa (Strensiq®, a long-term enzyme replacement therapy in patients with hypophosphatasia in childhood and adolescence; marketing authorisation under exceptional circumstances) was associated with the regulatory requirements for the pharmaceutical company to submit further comprehensive clinical data to the regulatory authority on the efficacy and safety of the pharmaceutical for evaluation. The pharmaceutical company was requested to establish a prospective registry to collect – among other things – data on the long-term efficacy and safety, as well as on the quality of life. The G-BA requested the pharmaceutical company to submit data from the registry as well as from the extension studies ENB-008-10 and ENB-009-10 and phase IIa study before the end of the time limit to assure safe evaluation of the extent of the additional benefit with regard to patient-relevant endpoints (mortality, morbidity, quality of life, and side effects) of long-term treatment with asfotase alfa. In the decision about the benefit assessment, there are three different patient groups.

For patients under five years, different single arm studies and one historical control were available. On the basis of the unadjusted comparison of the studies with the historical control – although associated with major uncertainties due to methodological limitations – positive effects were derived in the major patient-relevant endpoints „overall survival“ and „survival time without invasive ventilation“ and thus a non-quantifiable additional benefit can be expected. Comparative data on further endpoints or adverse events were not possible and quality of life data were not available.

It is not possible to collect the missing control data for this age group within the scope of a post-market surveillance, as – also in this age group – the natural course of perinatal and infantile hypophosphatasia is associated with a high mortality rate and severe symptoms which is also attributable to the fact that there are no adequate treatment options. Thus, it is not feasible to impose comparative data collection as a condition for the purpose of benefit assessment.

Much different is the age group of over 5-year-olds and patients with juvenile hypophosphatasia, respectively. In this group, besides single arm studies and a historical control group also data from a 24-week placebo controlled study with patients over the age of 13 years were available. Although data in the age group 5 to 12 years demonstrated changes from baseline in favour of asfotase alfa in the

endpoint growth as well as motor function, the results can only be interpreted to a limited extent due to the missing control and uncertainties regarding the clinical relevance of the mentioned endpoints.

In the comparative study, no statistically significant difference could be observed after 24 weeks of treatment with asfotase alfa in the age group of 13 to 66 year old patients in any of the patient-relevant endpoints (motor function, pain and disability) as compared to the untreated control group. The study duration was too short for this purpose. Only in the endpoint bone structure a difference was observed which must, however, be interpreted as a surrogate parameter. In these age groups of patients with juvenile HPP, further examinations would be significant within the scope of a registry for benefit assessment in order to e.g. demonstrate the functional improvement as a consequence of an enhanced bone structure on the basis of comparative data over a longer period.

However, the main uncertainties regarding asfotase alfa were attributable to the lack of control, in order to validly estimate the effect size in all endpoint categories.

Until 2019, no reevaluation of a substance onto which a registry study has been imposed as a condition could be subjected to a new benefit assessment for re-evaluation, as inclusion into the registries took much longer than expected. Also due to the fact that these obligations are not binding, physicians and patients might shy away from the documentation effort and decide against an inclusion into a registry study.

**Expectations regarding registry studies**

The above mentioned example shows that registries cannot answer all questions arising during benefit assessment. However, the goal should be to include all patients into the registry who are treated with the respective pharmaceutical in Germany. Alternatively, included patients must at least provide a representative selection and it must be comprehensible which patients have not been included into the registry. In the past, various academic institutions, HTA agencies, and regulatory authorities (EMA and FDA) were involved in the subject matter of registries. Among other things, a catalogue of criteria was developed in EUnetHTA for the evaluation of the quality of registries. This instrument comprises a three-step evaluation process concluding with an automated evaluation (see figure 3).

The systematic identification of confounders, consideration of known and unknown confounders, and recording of these characteristics in order to consider corresponding adjustments in the evaluations will remain the major challenges for the collection of not randomised data. The problem is that due to the severity of the disease, the expected or desired therapy effect, respectively, will cause a selection bias during patient selection in clinic practice and thus in data collection. Therefore, it would be all the more important to also identify those patients who do not receive this therapy. Selection bias can hardly be avoided, as data will be collected during the scope of post-market surveillance which is unblinded and normally not randomised.

It would also be important to focus on pragmatic, truly patient-relevant endpoints and previous and subsequent treatment, treatment duration, therapy discontinuations and its reasons are recorded in such a form that evaluation is possible within the scope of benefit assessment.

How a registry will be assessed as suitable on a case-by-case basis will certainly also depend on the prespecified questions. Whether it will be possible in future that registry operators can also interact with the G-BA to exchange details about the required quality criteria and potential adaptation requirements, remains an open question for the time being and it remains to be seen how the G-BA will deal

with these instruments he has been provided with. Especially the question as to for which substance and on the basis of which evidence the G-BA decides to impose a post-market surveillance in form of registries is relevant for the company's planning.

For if it is foreseeable that the affected substance might fulfil the selection criteria for post-market surveillance, an early interaction with the G-BA is possible. Under these conditions, it will certainly play a role how reliable the results of the major patient-relevant endpoints will be at the time of benefit assessment.

It must be considered whether there are uncertainties regarding the sustainability of the effects, whether predominantly only surrogate endpoints were measured and whether it is to be expected that in case of a longer study duration, the results of the surrogate endpoints might be reflected by patient-relevant endpoints. Besides insufficient statements on the patient-relevant endpoints and

**REQueST - Framework criteria for transparent quality evaluation of data collection in registries**

| Area | Item | Colour rating |
|---|---|---|
| **Methodological Information** | 1. Type of registry | |
| | 2. Use for registry-based studies and previous publications | |
| | 3.Geographical and organisational setting | |
| | 4. Duration | |
| | 5. Size | |
| | 6. Inclusion and exclusion criteria | |
| | 7. Follow-up | |
| | 8. Confounders | |
| **Essential Standards** | 9. Registry aims and methodology | |
| | 10. Governance | |
| | 11. Informed consent | |
| | 12. Data dictionary | |
| | 13. Minimum data set | |
| | 14. Standad definitions, terminology and specifications | |
| | 15. Data collection | |
| | 16. Quality assurance | |
| | 17. Data cleaning | |
| | 18. Missing data | |
| | 19. Financing | |
| | 20. Protection, security and safeguards | |
| **Additional Requirements** | 21. Interoperability and readiness for data linkage | |
| | 22. Data sources | |
| | 23. Ethics | |

Source: EUnetHTA, [online] https://eunethta.eu/request-tool-and-its-vision-paper/

Figure 3: A catalogue of criteria was developed in EUnetHTA for the evaluation of the quality of registries. This instrument comprises a three-step evaluation process.

too short a study duration, it can also be important whether patient populations that are highly relevant for the treatment of patients have not or only insufficiently been addressed in the study program. Furthermore, it must be investigated whether control data shall also be collected and for what period data shall be collected.

Therefore, the research question should be predefined as precisely as possible to enable collection of the missing data in a time-scaled and predictable manner. In the best case scenario, existing indication registries can be used. It must also be kept in mind that data collection must be suitable for the quantification of a potential additional benefit. If this can be ruled out a priori, further data generation does not seem reasonable. Thus, the number of procedures for which a post-market surveillance has be imposed as a condition is – from the present point of view – rather limited also against the background of the professional preparation that needs to be done beforehand.

**Conclusion**

The aim of post-market surveillance cannot be the general subsequent correction of deficiencies for previously unfavourable benefit assessment data or answer research questions that remained open during benefit assessment. It must be evaluated – also in consideration of the principles of proportionality and reasonableness – in which evidence situation, post-market surveillance shall be performed. Collected data must comprise major endpoints (both benefit and harm aspects) and must previously have been evaluated for a potential patient benefit to avoid under all circumstances wasting capacities and patient data for an incremental knowledge gain in the use of resources.

It is not reasonable to initiate a new data collection for already answered questions or those that are not relevant for the patient. Of course, it would be ideal to find a way to have a different level of evidence available as early as during benefit assessment. But if data collection is considered necessary, it is all the more important that the data quality is sufficient in order to quantify the additional benefit or identify new evidence gaps, where applicable.

The quality of data and their interpretability must not be discussed in different levels of stringency depending on positive or negative result. For this purpose, the provisions of the GSAV are very helpful, as the instruments can give a strong impetus to the obligations through subsequent negotiations of the reimbursement and limited circle of prescribers simultaneously causing the G-BA to substantiate their requirements.

Registry studies and registries are instruments for post-market surveillance to comparatively collect data in all endpoint categories (mortality, morbidity, quality of life and side effects).

Imposing conditions on the pharmaceutical company bears the risk that again mainly product registries will again be established for reasons of feasibility, although these should actually be avoided. A central registry office providing support with data management, evidence research and infrastructure would be ideal to structure the frayed registry landscape featuring compatibility issues, classification and standardisation issues and insufficient data quality and transparency.

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# Registry data of the GPOH by the example of the NHL-BFM study group

**Professor Birgit Burkhardt | Clinic for Paediatrics and Adolescent Medicine, Paediatric Haematology and Oncology, Münster University Hospital**

*The study groups of the Association for Paediatric Oncology and Haematology (GPOH) contribute to the systematic improvement of treatment outcomes for children and adolescents with a cancerous disease by means of consecutive therapy optimisation studies (TOS) and registries. Population-based recruiting and a sophisticated infrastructure of the participating centres and reference laboratories are important characteristics of these GPOH study groups. Essential requirements for the future use of the existing GPOH registry, as illustrated by the example of the NHL-BFM study group, for newly approved pharmaceuticals, are realistic and achievable case numbers as well as practicable and appropriate requirements for the organisation, administration, and financing of the existing registries.*

## Paediatric haematology and oncology in Germany

In Germany, approx. 2,500 to 3,000 children and adolescents are diagnosed with cancer every year. Boys are slightly more affected than girls.[1] The German Paediatric Cancer Registry that was established in 1980 and provides annual analyses of incidences and epidemiological data. Depending on the type of cancer, the typical age of onset varies, but in principle cancerous diseases occur at all ages of childhood and adolescence.

The most common subgroups include leukaemia (30 percent), CNS tumours (24 percent), lymphoma (14 percent), soft tissue sarcoma (6 percent) followed by peripheral nerve cell tumours, bone tumours, germ cell tumours, carcinoma, renal cell tumours, retinoblastoma, liver tumours, and other tumours making up less than five percent. Histological subgroups differ significantly from the common types of cancer in adults. In that age group, typical carcinoma only account for three percent of cancerous diseases in childhood and adolescence. Among other things, these differences make the treatment of children and adolescents with cancer significantly different from the treatment of adult patients.

## Dramatic improvements in the survival of children and adolescents with malignancies in Germany

Around 1940, the survival of children and adolescents suffering from cancer was below 20 percent regardless of the subtype of the cancerous disease; the only exception were Hodgkin lymphoma.[2] In 2010, the survival for neuroblastoma, brain tumours, rhabdomyosarcoma, acute myelogenous leukaemia, Ewing and osteosarcoma was approx. 60 to 80 percent and for acute lymphoblastic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), nephro-

blastoma (Wilms' tumour), and gem cell tumours even over 80 percent.

**Structured therapy optimisation by consecutive academic therapy optimisation studies**

The joint cooperative implementation of academic therapy optimisation studies (TOS) involving all treatment centres in Germany is essential for improving the survival rates.[3] Characteristics of TOS conducted by the Association for Paediatric Oncology and Haematology (GPOH) involve the use of combined cytostatic agents that are usually approved substances. In consecutive TOS, the current standard therapy is normally randomly adapted to individual research questions and evaluated prospectively.

In this way, a continuous systematic improvement of the standard therapy is achieved. The aim of the TOS is an optimised therapy in the sense of optimised patient outcomes. Unlike traditional clinical studies of the pharmaceutical industry, the goal is usually not to evaluate individual (new) substances or approve pharmaceuticals. Another characteristic of TOS by the GPOH is the population-based recruiting of all newly diagnosed patients for the respective TOS.

Upon the entry into force of the 12th amendment of the German Medicinal Products Act (AMG) in 2004, the implementation of academic TOS in paediatric oncology was considerably hampered which significantly slowed down the continuous optimisation process. This is due to the regulatory requirements and the resulting administrative effort associated with clinical studies, as no distinction is made between industry-sponsored „approval studies" and academic therapy optimisation studies with approved substances financed by public funding.

**GPOH and structures in paediatric oncology**

The Association for Paediatric Oncology and Haematology (GPOH) emerged from several working groups and was established as a scientific professional association in 1974. Among other things, the GPOH has elaborated and adopted guidelines for cooperative studies, the so-called GPOH study guidelines. These specify, among other things, that treatment in the field of paediatric oncology and haematology in therapy optimisation studies is considered as a standard of patient care at both national and international level. Moreover, they regulate and specify the assignment of the mandate for the study group direction stipulating that every study group direction shall be supported by a study commission.

Mandates are granted by election of the GPOH members and are limited in time. At present, approximately 30 GPOH study groups are active and take care of haematological diseases as well as all relevant oncological diseases.

**Characteristics of the GPOH study groups**

**Professor Birgit Burkhardt** *is specialist for Paediatrics and Adolescent Medicine with a focus on paediatric haematology and oncology. Since 2011, she is the head of the NHL-BFM study group and since 2019 she is the second deputy chair of the GPOH board. She works as a physician at the Clinic for Paediatrics and Adolescent Medicine, Paediatric Haematology and Oncology at Münster University Hospital.*

Regardless of the subtype of the cancerous disease and study group, most or all study groups, respectively, have common characteristics. The aim is the implementation of consecutive therapy optimisation studies to help improve therapy and outcomes.

Due to the administrative and financial requirements for the initiation and implementation of clinical studies since 2004, many study groups use registries to collect data and gain insights in rare subtypes, interim periods between clinical studies for the complete recruitment of all patients including those who did not fulfil the inclusion and exclusion criteria of clinical studies and for systematic long-term observation.

Study groups provide continuous and population-based recruitment (at least in Germany) including documentation of patient characteristics, diagnostics, therapy, and outcomes. For most of the study groups, documentation is performed using the remote data entry system Marvin. Data are compared with the paediatric cancer registry regarding completeness of the documented cases. In addition, the paediatric cancer registry carries out a long-term follow-up of patients and exchanges data with the study groups.

**Contribution of the G-BA agreement of 2007 for paediatric oncology**

The Agreement of the Federal Joint Committee about quality assurance measures for the inpatient treatment of children and adolescents with haemato-oncological diseases stipulates all other relevant aspects of patient care.[4] Purpose and objectives of the agreement comprise the assurance and improvement of structure, process and outcome quality, as well as assurance and improvement of both treatment and survival rate of patients aged 0 to 17 years with a paediatric haemato-oncological disease.

It determines the centres for paediatric haemato-oncological treatment and the infrastructure they must provide. It also includes the obligation for diagnostic backup through reference laboratories of the respective study group, inclusion of patients in clinical studies wherever possible, and the obligation to report patients to the paediatric cancer registries. All centres participating in the studies (and registries) of the GPOH must fulfil the so-called „G-BA criteria".

**Challenges and benefit of GPOH study groups by the example of the NHL-BFM group**

The NHL-BFM study group for patients with non-Hodgkin lymphoma (NHL) serves as a concrete example for the activities of a GPOH study group and the benefit registries provide. The study group's objectives include:

- Complete population-based registration of all newly diagnosed and recurrent NHL
- Improvement of outcomes for children and adolescents with NHL
- Systematic further development of the therapy within the scope of therapy optimisation studies
- Ensuring highly reliable diagnosis and therapy
- Assurance or improvement of patient safety, respectively
- Identification of therapeutically or prognostically relevant subgroups by means of translational research
- Integration of new substances within a reasonable time, especially
- for refractory and recurrent cases with unfavourable prognosis, and
- to reduce acute and long-term side-effects.

The NHL-BFM study group extends across Germany, Austria, Switzerland, and the Czech Republic. In Germany, some 55 centres are part of the NHL-BFM study group, the majo-

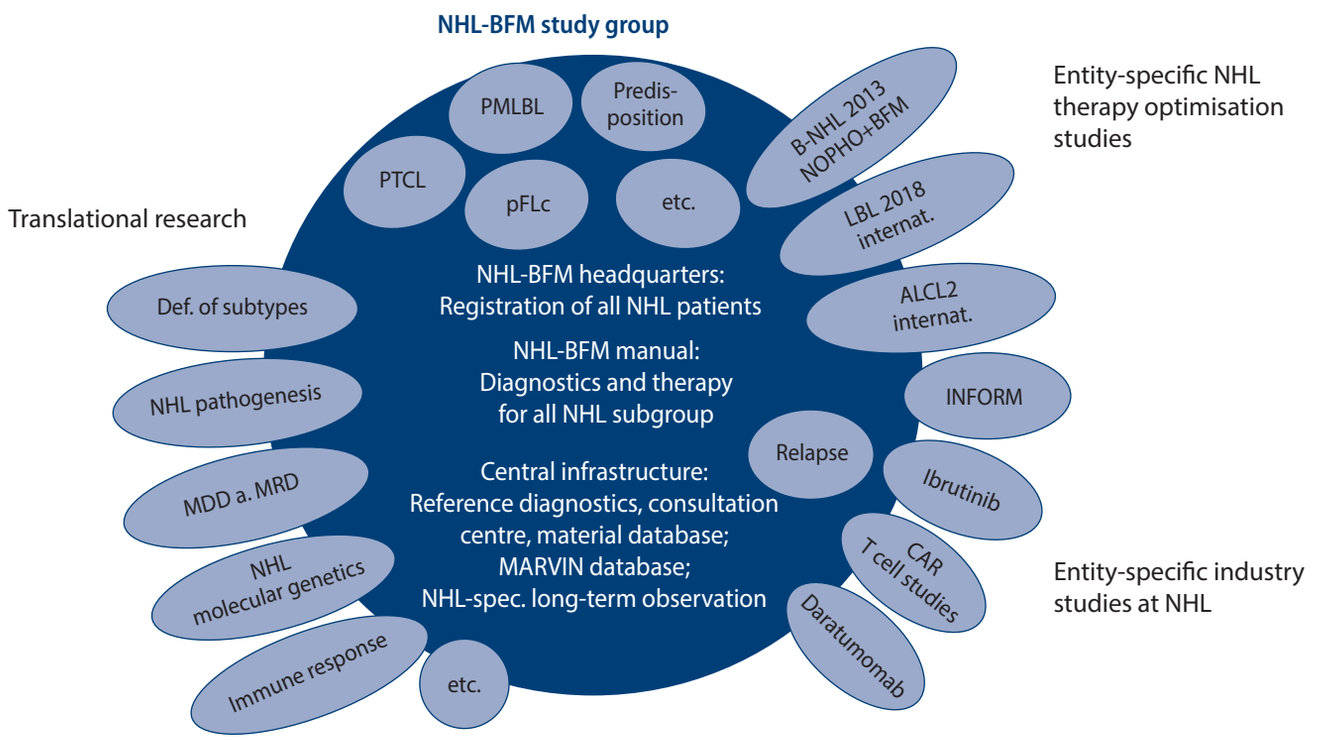
rity of which are haemato-oncological paediatric hospitals and departments of university hospitals, but also non-university hospitals.

**Organisational structure of the NHL-BFM study group**

Since 2011, the mandate for the central study unit of the NHL-BFM study group lies with Professor Birgit Burkhardt from the UKM Münster and Professor W. Wößmann from the UKE Hamburg; they are supported by the interdisciplinary NHL-BFM study commission. The core of the NHL-BFM study group is the NHL-BFM central study unit where all newly diagnosed patients are entered in the NHL-BFM Registry 2012 (see figure 1).

All participating centres get access to a summary of the gold standard of diagnostics and therapy of the individual NHL subtypes. The central infrastructure comprises reference laboratories for diagnostic backup which shall be achieved in all patients, an affiliated material bank, a cen-

**NHL-BFM study group structure (refer to the text for more details)**




Source: Prof. Dr. Dr. Birgit Burkhardt

Figure 1: In Germany, the NHL-BFM study group comprises approximately 55 centres. The majority of them are haematological-oncological paediatric hospital and departments of university hospitals, but also non-university hospitals.

tral registry database where participating centres complete registry-specific documentation forms (CRFs) via a remote data entry system, a long-term follow-up and – as another important element – a central help desk for all participating centres. In this way, recording of rare subtypes (e.g. PMLBL) and relapses is ensured. For larger subgroups, the NHL-BFM study group initiates clinical studies (TOS) with randomised research questions.

Studies like LBL 2018 are sponsored by academic institutions like the University hospital of Münster or the gGmbH of GPOH. Financial funding is granted by the German Cancer Aid or the German Childhood Cancer Foundation according to a peer-review procedure. Study data are pooled with the data of the NHL Registry. Patients with recurrent symptoms will be screened for their eligibility for pharma-sponsored approval studies (e.g. Ibrutinib) and recruitment pursued where applicable. Translational research projects, e.g. on the NHL pathogenesis, are affiliated with the NHL-BFM-Registry.

**Ensuring high-quality data in the NHL-BFM study group**

The quality of the data in the NHL-BFM study group is ensured at several levels. Table 1 shows a summary of various continuous measures taken for this purpose.

**Role of the NHL-BFM study group during drug development**

New substances with involvement of additional mechanisms of action can contribute to achieving the goals of the NHL-BFM study group, i.e. the improvement of survival rates and reduction of acute and long-term toxicities. For this reason, the members of the NHL-BFM study group actively participate in advisory boards and the Pediatric-Investigation-Plan (PIP) developments of the pharmaceutical industry on promising substances. The resulting pharma-sponsored studies will be made accessible to a few qualified centres through the five phase I/II networks of the GPOH. The NHL-BFM central study unit has a coordinating function. For NHL relapses, there is also the option to participate in the INFORM Registry (https://www.dkfz.de/de/inform/index.html).

In this project, tumour tissue is tested molecular genetically and the clinical relevance of the findings are discussed by an interdisciplinary expert panel.[5] Today, the NHL-BFM Registry already provides – to some extent – the possibility to trace outcomes and long-term effects after the application of new pharmaceuticals.

**Perspectives of the NHL-BFM study group**

In order to achieve the two ultimate objectives of improving survival rates and reducing acute and long-term toxicities for NHL patients – who would die quickly without therapy – continuation of the NHL-BFM Registry is essential for the NHL-BFM group. In order to improve survival rates of patients with an unfavourable prognosis and small subgroups, these patients need to have access to new substances.[6]

Delays in the approval of new substances for patients with recurrent symptoms lasting years or even decades are not acceptable against the background of survival rates of 20 to 30 per cent with current chemotherapy regimens. Involvement of the NHL-BFM group or European study groups into the prioritisation and trial design of PIPs guarantee that the focus remains on the patients' medical need. Thereby, the study groups can also support benefit risk assessment or indication, respectively, as relevant patient groups and their need can be characterised on the basis of evaluations of registry data. Moreover, study groups provide the infrastructure for diagnostic backup and trans-

## Selection of measures to ensure high-quality data

| Structural | Measures at the centres | Measures at the NHL-BFM headquarters |
|---|---|---|
| Entity-specific plausibility checks in the RDE system | Documentation by trained employees | Definition of goals and statistical plan |
| Use of an entity-specific "basic data set" over decades | Monitoring and audits within the scope of clinical studies | Structured documentation of defined data fields, if necessary additional medical letters or requests for consultation |
| | | Continuous central monitoring of the data quality and raising of queries |
| | | Case conferences at the study headquarters three times per week |
| | | Regular data analyses and presentation to participating centres |

Source: Prof. Dr. Dr. Birgit Burkhardt

Table 1: High-quality of the data is ensured at various levels – by means of structural measures at the participating centres as well as in the study headquarters.

lational research through the reference laboratories. Participating centres of the NHL-BFM study group are experienced and have been trained in the conduction of registries and clinical studies and the required infrastructure is available at the hospitals and secured by means of the „G-BA criteria".

A guiding factor in this respect might be the broad-based initiative „B-NHL Accelerate" in which patient representatives, international study groups, regulators, and the pharmaceutical industry plan the systematic review of substances for a certain subgroup of NHL relapses to prioritise, implement and make them available for patients using a concerted approach.[7] An early involvement of international NHL study group directors ensures a „needs-based" prioritisation independent of the results in adult patients and the orientation towards the mechanism of action and not only towards the histological entity.

Current discussions on the B-NHL Accelerate platform are mostly based on the data of international study groups generated in the registries. After the approval of new substances, these academic registries are available for the assessment of the relevance of the respective pharmaceuticals and patient outcomes. On the basis of the NHL Registry, the NHL-BFM study group offers, among other things:

- Knowledge of „medical needs"
- Established and well-known standard therapy in terms of effects and side-effects
- Sophisticated and stable infrastructure (diagnostics, documentation, qualification of study sites, after-care, etc.)
- High data quality

- Population-based recruiting
- International collaborations with long-time partners.

The two essential requirements for the future use of existing GPOH registries, as illustrated by the example of the NHL-BFM study group, for the evaluation of pharmaceuticals that received conditional approval, are statistical plans and case numbers that are achievable within a reasonable time as well as practicable and appropriate requirements for the organisation, administration, and financing of existing registries. It is important to avoid rigid requirements that do (can) not consider the individual context of the respective registry and that would be equivalent to those of clinical studies and inevitably lead to delays in the accessibility of new substances for children and adolescents with cancerous diseases.

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# NeuroTransData Registry by the example of multiple sclerosis

**Professor Stefan Braune – Head of NTD RWE Data Management | Dr Arnfin Bergmann – CEO of NTD**

*NeuroTransData GmbH is a network of physicians in the field of neurology and psychiatry throughout Germany. As a pioneer in digitalisation and personalised medicine, the NTD network has been running a registry data base since 2008 with a high data density and quality through the use of suitable technical and organisational measures. The data base represents the basis of innovative developments for optimised patient care. During the past years, methods for the analysis of real world data (RWD) have improved significantly so that data on real world evidence (RWE) can achieve a standard comparable to clinical studies in terms of quality, validity and robustness.*

**NeuroTransData Physician network**

NeuroTransData GmbH is a network of physicians in the field of neurology and psychiatry throughout Germany. Members are from modern, highly effective and fully digitalised practices with a large patient base and a cluster distribution across Germany. The company currently has 66 practices and 133 members. Over 600 000 patients are treated at practices within the physician network every year. The objective of the physician network is a high standard of treatment for every patient through the use of modern technology and treatment methods.

The foundation of this network operated by physician for physicians and patients is both its commitment to optimise patient care by means of innovative solutions and to better understand and use data collected within the scope of their daily clinical practice. The NTD network is a pioneer in the digitalisation of personalised healthcare and has been running a registry database since 2008, currently active on the indications of bipolar disorders, dementia, epilepsy, migraine, multiple sclerosis (MS), Parkinson's disease and motor disorders, and schizophrenia. One focal point is the MS database, in which some 25 000 MS patients are currently being recorded over an average observation period of 5.1 years.

**DESTINY – DatabasE-assiSted Therapy decIsioN support sYstem**

Since 2012, the network has been developing further modules in addition to the basic structure of the database in support of physicians and patients in everyday practice. The aim is to improve the interaction between physician and patient and gather healthcare data for the purposes of continuous therapeutic control and optimisation. Against the background of this idea, the physician network NTD

has developed a comprehensive concept: DESTINY (see figure 1).

Today, DESTINY contains a set of different modules to support physicians and patients (i.e. treatment optimisation, medication interactions, prediction of the course of the disease, biomarker testing, patient portal with bidirectional data exchange).

DESTINY guarantees a high-quality and transparent treatment at lower costs (reduction of hospital admissions and physician visits, reduction of medication costs). With this data, additional scientifically interesting questions in healthcare research can be addressed. DESTINY is not only limited to multiple sclerosis, but is also scalable to other disease areas.

**NTD registry data base:**
**Background information**

The core of DESTINY is the web-based NTD registry database, which has received pseudonymised patient data in relation to diagnosis, treatment and quality of life, side effects and reasons for changes in treatment since 2008. The database was developed in collaboration with the Ludwig Maximilian University (LMU) in Munich and evaluated and approved by the Ethics Committee of the Bavarian State Chamber of Physicians in 2012. This approval was re-confirmed by the Ethics Committee of the North-Rhine State Chamber of Physicians in 2017.

Web-based since 2013, the registry database is a modular system containing basic documentation and a multitude of specialist modules (healthcare module, register module, study module, patient module, administration module, etc.). All data collected is taken systematically at each participating practice and saved to the database. Statutory data protection requirements, in particular the German Federal Data Protection Act (BDSG) and the EU General Data Protection Regulation (GDPR) are ensured through an appropriate consent and encryption process. The healthcare and register modules have a standard disease-specific

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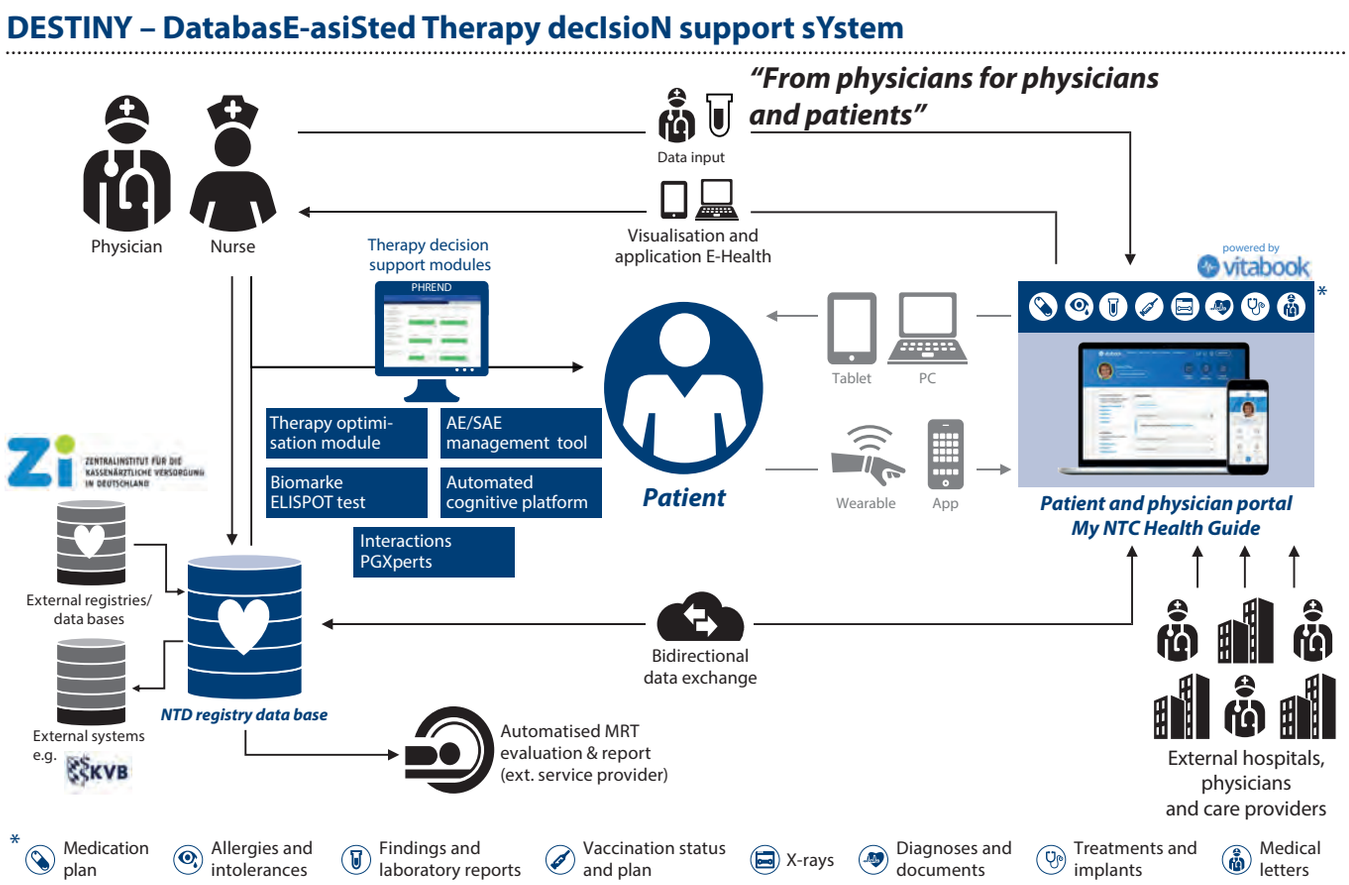
**Dr Arnfin Bergmann** *is neurologist and psychotherapist. After his medical studies he worked at the hospital for several years and then changed to the pharmaceutical industry for a short time. In 1995, he opened his own practice where he works as director. Since its foundation in 2008, he has been director of physician network NeuroTransData (NTD).*




Source: NeuroTransData GmbH | NeuroTransConcept GmbH

Figure 1: The core of DESTINY is the registry database with various modules that has been developed with the aim of supporting physicians and patients in everyday practice.

basic documentation, whereas additional assessments for partial database collections are reflected in the study module. For the purposes of standardisation, medications are recorded according to current ATC (Anatomical Therapeutic Chemical) classification and diagnoses according to the current version of ICD-10 (International Classification of Diseases). For the purposes of treatment monitoring and support, disease progression and treatment procedures are displayed to the attending physician for each individual patient. The administration module manages system users, practice master data, studies, and metadata. The patient module allows for active inclusion of patients in the treatment process via electronic surveys.

The appropriate technical and organisational measures

are taken to ensure confidentiality, integrity, availability, authenticity, reviewability and transparency with regard to the registry database. For the purpose of data quality control, practice-oriented protocols and queries are displayed on the online registry database and edited by the practices. The registry database is updated continuously, being adapted and expanded to meet clinical practice requirements. Due to its modular design, the system can easily be extended to cover other indications and areas of application.

The following indications are currently available on the NTD database:

- Bipolar disorders
- Dementia
- Epilepsy
- Migraine
- Multiple sclerosis
- Parkinson's disease and motor disorders, and
- Schizophrenia.

**Quality assurance measures during data collection**

Every working day, employees of the NTD practice network enter data into the registry database. In addition, data from external sources can be imported. Various measures ensure the high-quality of the data as illustrated in the following section.

**Continuous education for quality assurance during data collection**

Physicians and healthcare professionals of all participating practices receive continuous education and special training in the handling of the database and the associated modules. Webinars are complemented by face-to-face events and workshops during the annual NTD district meeting. Specially trained database nurses work at every centre to ensure an optimised use of the database and high-quality data. Moreover, active use of the database has been incorporated as a quality criterion into NTD's statue that is evaluated by an external certification authority during an annual audit.

In addition to their database-specific education, all documenting nurses and neurologists have an up-to-date GCP qualification. For the recording of complex instruments, e.g. EDSS (Expanded Disability Status Scale), specific training and qualification requirements must be met.

**Automatic quality assurance measures**

Data quality will be evaluated and monitored by the Data Management Team of NeuroTransData. In addition, the Analytics Team of PricewaterhouseCoopers (PwC) performs additional evaluations.

**Evaluations in the front end during data input**

The web front end for data input and editing (user interface, UI) is characterised by three different types of data input:

**1. Drop-down list:** A pre-defined list of different options is provided to the user from which he can choose none or exactly one value. The presentation is based on the number of options to be displayed. In case of a small number, a group of buttons and in case of a large number, a drop down menu is displayed. Wrong entries – such as the input of two or a wrong value – are thus impossible.

**2. Multiple selection:** A series of different options is displayed as a group of buttons. The user can choose none, one or multiple options at the same time.

**3. Free text input:** An entry field is displayed where a value can be entered. Apart from a few exceptions, these include dates or numbers. For numbers, a note is displayed as a placeholder indicating minimum and maximum va-

lues as well as increments. With a regular expression, the content will be verified upon data entry. Incorrect values will not be accepted; saving a module – with all input and selection values – is prevented as the module's save button is deactivated.

Through this protection of individual fields against the input of wrong values, simple dependencies of two data fields can be reflected within a module and verified automatically. This applies in particular to field pairs where contradictory entries can be made. By defining these dependencies, fields can be shown or hidden dynamically, if any other field assumes any desired or a certain value.

**Back end verification after data entry**

In more complex relationships, verification of the plausibility of certain data field depending on one or more other fields are not possible in the front end. These verifications are performed on a weekly basis using automated script programs on the central database server (back end). These programs use SQL (structured query language) and are run directly on the Database Management System (DBMS) where they generate relevant queries. In exceptional cases – in case of very complex calculations – evaluations using programs in higher programming languages can be used.

Evaluation results (queries) will be displayed as a verification protocol upon opening the registry at a position where the practice can easily see them. These verification protocols can then be processed by trained database-nurses and physicians.

**Quality assurance measures during data analysis**

Extraction and analysis of data for NTD's scientific projects are performed in collaboration with Pricewaterhouse Coopers (PwC) in Zurich, Switzerland. A team of highly-skilled mathematicians and statisticians thoroughly assesses all extracted data sets externally for data density, data consistence, plausibility, and entry errors, before such verified and qualified data is then used for scientific analyses. For this external quality assurance by PwC, standardised processing and documentation protocols are available.

Besides project-specific measures for external quality assurance, data quality of the indication-specific NTD registry is reviewed by PwC on a continuous basis. The results are integrated into the continuous process for quality improvement during data documentation and collection within the NTD network.

The reduction of potential risks as a central powerful quality assurance tool plays an important role. All processes will be examined from data input until evaluation of the results:

- Functionality of the systems
- Data input and transfer
- User behaviour and actions
- Descriptions, instructions, data field designations.

Risk classification is performed on the basis of a risk matrix with the goal to derive suitable measures for risk minimisation and thus reduce the probability of critical risks as much as possible.

**Data protection**

**Informed consent**

The NTD database is an integral part of a high-performance data security system that was developed in collaboration with the Ludwig Maximilian University (LMU) in Munich and evaluated and approved by the Ethics Committee of the Bavarian State Chamber of Physicians in 2012.

This approval was re-confirmed by the Ethics Committee of the North-Rhine State Chamber of Physicians in 2017. Statutory data protection requirements, in particular the German BDSG and the European GDPR, are ensured

## Risk matrix (1)

| Probability (related cases) | Severity of harm (S) | | | |
|---|---|---|---|---|
| | Negligible (S1) | Minor (S2) | Moderate (S3) | Major (S4) |
| P5 frequent | IFRM (5) | ITL (12) | ITL (15) | ITL (20) |
| P4 probable | ACC (4) | IFRM (10) | ITL(12) | ITL (16) |
| P3 occasional | ACC (3) | IFRM (8) | IFRM (9) | ITL (12) |
| P2 remote | ACC (2) | ACC (4) | IFRM (6) | IFRM (8) |
| P1 probable | ACC (1) | ACC (2) | ACC (3) | ACC(4) |

| Risk Evaluation Score | Definition | Abbreviation |
|---|---|---|
| 1–4 | Acceptable | ACC |
| 5–9 | Investigate Further Risk Mitigation | IFRM |
| 10–20 | Intolerable, unacceptable | ITL |

Source: NeuroTransData GmbH | NeuroTransConcept GmbH

Table 1: Risk classification is performed on the basis of a risk matrix with the goal to reduce the probability of critical risks as much as possible by means of quality assurance measures.

through an appropriate consent and encryption process.

The NTD registry database is used to identify suitable patients for studies, perform evaluations across patients in healthcare research settings, address health economic questions, and establish a link to clinical studies and observational studies using a single source approach. Personal patient data is processed on the basis of a consent (Article 6 para. 1 lit. a, Article 9 para. 2 lit. 6 BDSG) and stored on a long-term basis. If a patient withdraws, no further data will be collected and already collected data will be anonymised and used without any possibility to identify the individual patient. In case of anonymisation, any direct assignment of the data to the individual is excluded. Upon withdrawal, the patient can request removal of his/her data in the database. In the event that NTD ceases the operation of the registry, use of the data will pass to the legal successor or a scientific-medical professional association.

**Anonymisation process**

**Abbreviations:**

**AID** Identification number of the attending physician

**KID** Data of a pre-defined collective

**IDAT** Identifying patient data

**MDAT** Medical data of the patients
**OrgDat** Master data of the practices and other data collection centres
**PID** Patient identification number
**PToken** Patient access code
**UID** User ID of a patient as user of the Data Repository
**VDB** Treatment database

The encrypted patient list with IDAT and the treatment database (VDB) with MDAT are operated separately. An identification number is assigned to every patient stored in the Data Repository together with the IDAT, i.e. PID. The attending physician knows the PID that serves as a clear link between primary data with Data Repository. The attending physician (AID) can only access the treatment module within the treatment context. The AID is managed in the organisation database. Normally, it is assumed that there is only one attending physician. Therefore, the attending physicians will get access to the entire MDAT in any form of processing with the respective authorisation. MDAT is always accessed via the patient list.

NeuroTransData GmbH only accesses the treatment module for administration purposes. IDAT will be stored centrally in encrypted form. The symmetric encryption method used is AES 256 as recommended by the Federal Office for Information Security (BSI). Only the attending physician knows the encryption key. Any decoding of the IDAT by NeuroTransData GmbH is thus ruled out. The keys will be managed by an external trust centre at the Ludwig Maximilian University in Munich. For data extraction and transmission to external third parties (e.g. independent statistical institute) the following process is used:

**1.** Only MDAT are extracted,
**2.** The initial PID is replaced by a random value.

By only extracting MDAT and replacing PID by a random value, NTD ensures the complete anonymisation of data.

**Data quality**

Through the integration of data collection into the clinical practice of patient care, a consistently high data density and quality has been achieved. Continuity of data collection can be documented on the basis of the key figures as illustrated in table 2.

**Analyses and evaluations**

All data collected since 2008 is used for treatment research. For this purpose, data is extracted for the respective research question in pseudonymised form, pooled and anonymised using the above mentioned processes. Due to the high data density and long follow-up period, even complex questions can be evaluated with qualified and validated statistical methods (e.g. comparative efficacy analyses of pharmaceuticals, variations in the characteristics of patient cohorts, socio-economic effects of these variations in the care landscape). For years, NTD/NTC has been supporting e.g. AMNOG (German Pharmaceutical Market Reorganisation Act) procedures for price determinations of new pharmaceuticals with real world data.

Scientific projects are regularly presented at national and international congresses and published in prestigious scientific journals. In recent years, the NTD/NTC initiated joint projects with academic and medical institutes throughout Germany. Moreover, the NTD registry dates form the basis for ambitious NTD projects, such as prediction of therapy efficacy in every individual patient with relapsing multiple sclerosis (PHREND®) (see figure 2).

Extensive analyses using established mathematical-statistical methods confirm the validity of the prediction for every individual patient with regard to the expected efficacy of the respective available medication. The example

**Patients with relapsing MS in the NTD MS Registry between 2010 and 2018 with key figures of continuously documented data density over the years**

| Index Year | Number of RRMS patients | Documented visits per year | DMT cycles per year | Episodes per year | MRI scans per year |
|---|---|---|---|---|---|
| 2010 | 5,286 | 16,647 | 4,564 | 1,846 | 3,137 |
| 2011 | 6,752 | 24,593 | 5,840 | 2,676 | 4,021 |
| 2012 | 7,126 | 23,620 | 6,289 | 2,636 | 3,117 |
| 2013 | 7,621 | 26,141 | 6,489 | 2,463 | 3,866 |
| 2014 | 7,679 | 28,574 | 7,635 | 2,094 | 3,978 |
| 2015 | 8,153 | 28,615 | 7,503 | 1,988 | 3,842 |
| 2016 | 8,372 | 29,694 | 7,496 | 1,776 | 3,688 |
| 2017 | 8,904 | 30,834 | 7,724 | 1,641 | 3,415 |
| 2018 | 8,532 | 28,917 | 7,182 | 1,261 | 3,427 |
| 2010–2018 | 17,079 | 237,635 | 13,272 | 18,381 | 32,491 |
| Mean/year *per patient | 7,603 | 3.47* | 6,747 | 0.27* | 0.47* |
| Standard deviation | 1,105.43 | 2.44 | 1,056.49 | 0.59 | 0.71 |

RRMS = relapsing-remitting-multiple sclerosis; DMT = disease modifying therapies; MRI = magnetic resonance imaging

Source: NeuroTransData GmbH | NeuroTransConcept GmbH

Table 2: The integration of data collection into the clinical practice of patient care is reflected by the key figures of the continuously documented data density over the years.

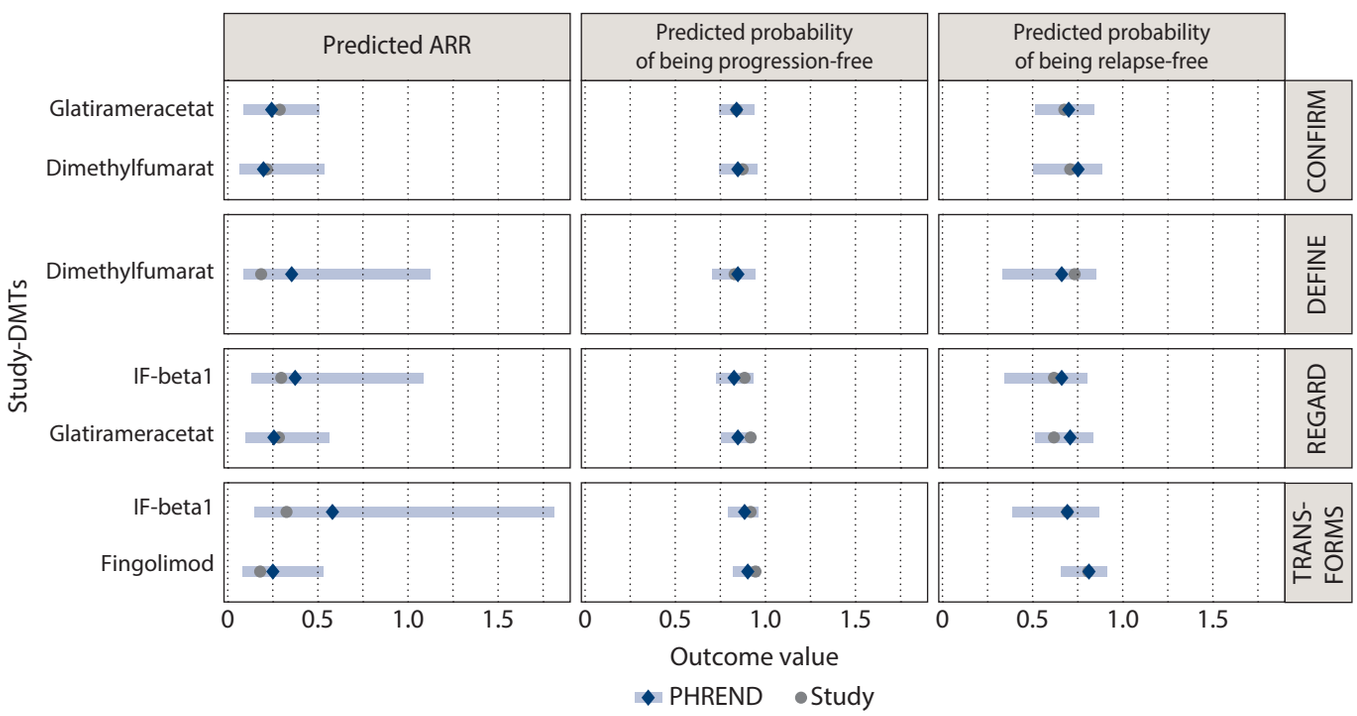
shows PHREND®'s prediction for the efficacy as compared to the actual results of clinical studies demonstrating a high correlation of these results for the respective comparable patient cohorts.

**Outlook**

Current steps of the approval authorities at national and European level will make the quality of existing indication-specific registries transparent and verifiable and thus comparable. Quality criteria will evolve that will be defined as a prerequisite as to which complexity level of the analysis and what significance of the results will be qualified and validly possible. The example of the suggested Eunethta Wp5b criteria demonstrates the quality of the NTD registry. Figure 3 shows the self-assessment of the NTD MS registry by the example of the EUnetHTA WP5b standard.

All assessments are performed on the basis of the quality management documentation that has been developed

**PHREND® predicted outcomes vs study outcomes of CONFIRM, DEFINE, REGARD, TRANSFORMS**




Source: NeuroTransData GmbH | NeuroTransConcept GmbH

Figure 2: The results of PHREND's calculated prediction for the efficacy of the available pharmaceuticals as compared to the actual results of clinical studies confirm the validity of the prediction.

for the NTD MS registry, including SOPs for all procedures of data collection, data management and storage, and pseudonymisation of individual patient data, in collaboration with the Ludwig Maximilian University (LMU) in Munich, as well as quality assurance measures during extraction and analysis of real world data in collaboration with our PwC partners. The data management of the NTD MS registry received a favourable vote by the ethic committees of the Bavarian and North-Rhine State Chamber of Physicians.

On the basis of such defined qualified data together with the statistical methods that have been developed in recent years for the analysis and control of data structures, real world data can be used on a scientifically substantiated, validated and robust basis for comparative benefit assessments in the actual application of substances in the market, comparisons with single-arm study populations with „matched" comparable real world patient cohorts with other active substances, as well as any other socio-economically innovative procedures, such as value based

## Evaluation of the NTD MS Registry with the EUnetHTA WP5b standards in registries draft tool

| Area | Item | Individual score | Area score | Maximum score |
|---|---|---|---|---|
| **Methodological Information** | 1. Type of registry | 2 | **14** | 14 |
| | 2. Objectives and research questions | 2 | | |
| | 3. Setting | 2 | | |
| | 4. Duration | 2 | | |
| | 5. Size | 2 | | |
| | 6. Inclusion and exclusion criteria | 2 | | |
| | 7. Follow-up | 2 | | |
| **Essential Standards** | 8. Registry protocol | 2 | **23** | 24 |
| | 9. Governance structure | 2 | | |
| | 10. Quality assurance | 2 | | |
| | 11. Financing | 2 | | |
| | 12. Data collection | 2 | | |
| | 13. Minimum data set | 2 | | |
| | 14. Data dictionary | 2 | | |
| | 15. Standad definitions, terminology and specifications | 2 | | |
| | 16. Confounders | 1 | | |
| | 17. Data cleaning | 2 | | |
| | 18. Protection, security and safeguards | 2 | | |
| | 19. Informed consent | 2 | | |
| **Additional Requirements** | 20. Interoperability readiness | 1 | **5** | 6 |
| | 21. Data sources | 2 | | |
| | 22. Ethical committee | 2 | | |

eunethta
EUnetHTA
WP5b standars
in regestries draft tool

NTD
Centers of excellence
NeuroTransData

Source: NeuroTransData GmbH | NeuroTransConcept GmbH

Figure 3: Eunethta criteria allow for transparent verification of the quality of indication-specific registries.

payment models (see figure 4). Long-term lively data collection in clinical practice can only be successful, if these direct advantages can be achieved for the involved physicians and patients in everyday treatment and thus provide a continuous intrinsic motivation for data collection.

This process must be supported by user-friendly, largely automated processes using state-of-the-art IT structures.

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[1]Over the past ten years, many scientific and socio-economic assessments arose from the collaboration of NTD and PwC as well as academic institutions and research-based pharmaceutical companies on the basis of the NTD patient registries.

During discussions at scientific meetings and symposia the results are generally reported in presentations, posters, and publications. Please refer to the below publications:

**Basic principles of registries**

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(2018). Characteristics of MS Patients Treated With PR-Fampridine in a Real-world Setting Based on the NeuroTransData Network in Germany. Poster for 35th Congress of the European Committee for Treatment and research in multiple sclerosis (ECTRIMS), 10-12 October 2018, Berlin, Germany.

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Bergmann A, Braune S, Rossnagel F (2019). „Nutzung der innovativen digitalen Plattform DESTINY zur Durchführung von prospektiven, nicht-interventionellen Studien am Beispiel von CLADBRAVE (Effect of CLADriBine treatment on pharmacoeconomic parameters and social resources in a ReAl-world environment)." (Use of innovative digital platform DESTINY for the conduction of prospective, non-interventional studies by the example of CLADBRAVE (Effect of CLADriBine treatment on pharmacoeconomic parameters and social resources in a ReAl-world environment). Poster for 92nd Congress of the German Society for Neurology (DGN)", 25-28 September 2019, Stuttgart, Germany.

Körwer M, Peikert A, Dikow H, Wehrle K, Rossnagel F, Hägele M, Bönig M, Schnabel S, Bergmann A, Braune S (2019). NeuroTransData Headache Registry: Digital platform for interactive patient management and healthcare research. Poster for 92nd Congress of the German Society for Neurology (DGN)", 25-28 September 2019, Stuttgart, Germany.

Bergmann A, Braune S, Dikow H, Roßnagel F (2019). Trends in disease-modifying therapies´ (DMTs) use and efficacy between 2010 and 2017 in outpatients with relapsing-remitting-multiple-sclerosis (RRMS) in Germany. Poster for 35th Congress of the European Committee for Treatment and research in multiple sclerosis (ECTRIMS), 11-13 September 2019, Stockholm, Sweden.

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# Registry data in neuromuscular diseases: SMArtCARE Registry

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*Spinal muscular atrophy (SMA) belongs to the so-called rare diseases, yet is considered one of the most common genetic causes of death in childhood. New pharmacotherapies can have a sustained effect on the course of the disease. However, the evidence available at the time of approval is rather limited in most cases. SMArtCARE is a disease-specific database for the collection of data on standardised follow-up examinations of SMA patients. Data analysis is performed independently of pharmaceutical companies under the supervision of a steering body of clinicians and patient representatives. SMArtCARE can make a major contribution to the evaluation of the long-term efficacy and safety of different therapies.*

## Introduction

Neuromuscular diseases belong to the group of rare diseases. Besides Duchenne's disease, spinal muscular atrophy (SMA) is one of the most common neuromuscular diseases with childhood onset. SMA is an autosomal-recessive disease mostly due to a homozygous deletion of the SMN1 (survival motor neuron) gene. The resulting lack of the SMN protein mainly affects the motor neurons in the spinal cord resulting in a progressive loss of muscle strength. The incidence of SMA is approximately 1:7,500 newborns.[1,2] SMA is divided into different types by the age at symptom onset and the maximum motor function achieved during the natural course of the disease (see table 1).

The varying degrees of severity of the disease is particularly due to the number of existing SMN2 copies. The SMN2 gene is a substantially homologous copy of the SMN1 gene differing in particularly through a base substitution of a splice site in exon 7. In healthy individuals, SMN2 has no significance, while in SMA patients SMN2 can partially compensate the missing SMN1. Since every individual has a different number of SMN2 copies, this number of copies is a key factor for the amount of produced SMN protein and consequently the degree of severity of the disease. The more SMN2 copies an individual has, the milder the course of the disease will be.

However, the number of SMN2 copies does not always allow for a reliable prognosis, as other – partly unknown – factors also have an influence on the course of the disease. The severe form of SMA (type 1) is the most common form and – if left untreated – leads to death within the first two years of life in most cases due to the patients' respiratory insufficiency. Up to now, SMA was thus among the most common genetic causes of death in childhood.

## Classification of spinal muscular atrophy

| Type of SMA | Onset of symptoms | Natural course of the disease | Number of typical SMN2 copies | Incidence at birth |
|---|---|---|---|---|
| Type 0 | Prenatal | Not viable | 1–2 | <5 % |
| Type 1 | <6 months | No independent sitting, require respiratory intervention within the first two years | 2(–3) | 60 % |
| Type 2 | 6–18 months | Independent sitting, but inability to walk unaided, intermittent ventilation | (2–)3(–4) | 25 % |
| Type 3 | 18 months–18 years | Free walking that can be lost again | 4–5 | 10 % |
| Type 4 | >18 years | Free walking | 4–6 | <5 % |

Source: Prof. Dr. Janbernd Kirschner

SMA is divided into different types by the age at symptom onset and maximum motor function achieved during the natural course of the disease.

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**Medical treatment of SMA**

Drug-based therapeutic approaches for the treatment of SMA pursue different strategies. Causal therapies aim at increasing the production of the SMN protein. This is achieved either by modification of the SMN2 splice or replacement of the missing SMN1 gene. Other therapy approaches do not aim at intervening directly in the production of the SMN protein, but aim at achieving an enhanced muscle function by means of other, non mutation-specific measures.

In 2017, the EMA approved nusinersen as the first specific therapy for the treatment of SMA. This splicing-modifier (antisense oligonucleotide) is administered intrathecally every four months after an initial loading phase. The approval of nusinersen was based on two double-blind, placebo-controlled studies on the treatment of SMA type I in early infancy[3] and SMA type II in childhood.[4] However,

therapy was then approved for all patients with spinal muscular atrophy regardless of their age, degree of severity or disease stage. This means that the vast majority of patients who currently receive treatment remains outside the study populations with regard to age and/or disease stage.

Gene replacement therapy using an adeno-associated virus is another therapy approach. The respective pharmaceutical preparation onasemnogene abeparvovec (trade name: Zolgensma)[5] was approved by the FDA in 2019 for the treatment of paediatric SMA patients aged < 2 years. In this case, the approval was also based on subpopulation with a very low number of patients. This gene therapy comprises one single intravenous infusion. So far, there is only limited experience regarding the long-term efficacy and safety of the treatment. Another orally administered splicing modifier (Risdiplam)[6] is currently in an advanced clinical development stage. Due to the rareness of the disease, further randomised studies in other patient collectives or comparative studies between the pharmaceuticals are currently not planned.

Apart from the different pharmacotherapies it becomes obvious that especially the time of treatment initiation is of vital importance for the therapeutic benefit. This becomes particularly apparent in case of presymptomatic treatment initiation. Almost all patients with SMA have an asymptomatic interval after birth. Depending on the degree of severity, this stage can last for weeks, months, or years. First studies evaluated treatment initiation during this presymptomatic stage.

Looking at the group of patients with two SMN2 copies only – who are considered most likely to develop type I – 12 of 15 patients with two SMN 2 copies achieved „walking alone" as a result of early initiation of nusinersen treatment (NURTURE study)[7], while none of the infants achieved „walking alone" when treatment was initiated after symptom onset (ENDEAR study).[3]

These findings gave rise to the call for the inclusion of genetic testing for SMA into the general newborn screening. First results of a pilot project in Germany during which more than 150 000 newborns were screened seem to confirm the reasonableness of such a screening program.[1]

**Establishment of the SMArtCARE registry**

The idea of systematic data collection of – ideally – all SMA patients evolved as a consequence of the expected availability of various pharmacotherapies for the treatment of SMA in combination with the limited evidence at the time of approval. Even if such a registry cannot replace randomised studies, registry data can in fact make a major contribution to the evaluation of the long-term efficacy and safety of the new therapies providing the best available evidence. Moreover, the concept of a disease-specific – as opposed to product-specific – registry facilitates comparison between various therapies. The potentially high number of documented patients as well as the common evaluation with data from other countries provides further opportunities.

The SMArtCARE registry (www.smartcare.de) was established for German-speaking countries by neuropaediatricians and neurologists in collaboration with patient organisations.[8] It is a disease-specific registry, so that the only inclusion criteria are a confirmed genetic diagnosis of SMA (SMN1 mutation) and the informed consent of patients or their legal guardians, respectively. Patients are included by the participating treatment centres. Initially, the registry was established with financial support of Biogen. In future, funding of the registry shall be secured with the support of other sponsors and public funds.

**Scope of data collection**

In the SMArtCARE database, symptoms and pharmacotherapies of SMA patients are documented over time. As it is not an interventional study, only data about the clinical routine of the treatment centres are recorded. In accordance with international consensus, recommendations for the clinical follow-up of SMA patients were derived from SMArtCARE (table 2).

For the documentation of the motor function, various standardised tests were selected that are validated for the respective SMA disease stage. Moreover, data on the respiratory situation and swallowing function as well as adverse events and unscheduled hospital stays were also documented.

In case of termination of the data input, the respective reasons were recorded (e.g. death, lost to follow-up, withdrawal of consent). Thus, the database enables a comprehensive evaluation of morbidity and mortality relating to various therapeutic interventions.

**Database and quality assurance**

For the SMArtCARE data collection, a web-based platform for electronic data capture (EDC) was developed in collaboration with OpenApp Ltd (Dublin, Ireland). Data is stored on a server at the University Hospital Freiburg. Various standardised report forms (eCRF) are available for data input. Whenever possible, there are pre-defined response options in the individual data fields.

As far as reasonably possible, plausibility checks are performed at the stage of data input already, in order to avoid incorrect entries. All data entries and modifications are documented with reference to the logged-in user and time. In order to allow data sharing with other databases, standardised data fields are used. Within the framework of pseudonymisation, identifying data is stored in a separate database. As a result, international pseudonymisation tools (e.g. EUPID) can be used later to identify identical patient records between various registries. Especially for rare diseases, this is of increasing importance. The SMArtCARE databases fulfils the requirements of the German General

## Recommended follow-up intervals for SMA patients

| |
|---|
| **Baseline documentation (first follow-up visit)** |
| **Current treatment and findings (every follow-up visit)**<br>■ Incl. motoric milestones in children < 12 years |
| **CHOP INTEND test**<br>■ All children < 2 years<br>■ Patients > 2 years only in case of lost ability to sit |
| **Bayley-III test (motoric part)**<br>■ Children < 2 years if CHOP INTEND > 50 points |
| **HFMSE**<br>■ All patients able to sit independently > 2 years<br>■ If CHOP INTEND > 50 points: CHOP INTEND and HFMSE**<br>■ If CHOP INTEND > 60 points: HFMSE instead of CHOP INTEND |
| **RULM test**<br>■ All patients able to sit independently > 2 years (in wheelchair) |
| **Six-minute-walking-test (6-MWT)**<br>■ All patients able to walk unaided > 3 years |
| **ALS Functional Rating Scale (adults)** |
| **Pulmonary function** |
| **Documentation of adverse events** |

CHOP-INTEND: The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HMSE: Hammersmith Functional Motor Scale Expanded; RULM: Revised-upper-limb-module; 6-MWT: Six-minute-walking-test

Source: Prof. Dr. Janbernd Kirschner

SMArtCare recommendations for clinical follow-up of SMA patients.

Data Protection Regulation (GDPR) and was approved by the competent data protection officers and ethics committees. It was registered with the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS) under registration number DRKS00012699).

In addition to data collection, the platform shall also facilitate patient care in consideration of the published treatment recommendations.[9,10] Based on the entered clinical data, the system suggests evaluation instruments that seem reasonable in this specific case. Moreover, intervals for the next follow-ups are recommended. The completed report forms can be printed out for documentation in the patient record. Documented side-effects can also be printed out and submitted directly to the Medicines Commission or other competent authorities. For every patient, the system provides a chronological overview of motor function tests, therapeutic measures, pharmacotherapies, and adverse events. Just in time before patients reach the legal age, the system automatically indicates the need for an updated informed consent.

In order to optimise inter-rater reliability, SMArtCARE offers training workshop for physiotherapists and physicians on standardised tests for the documentation of the motor function four times a year. During these workshops, other aspects of therapy optimisation for SMA patients are also addressed.

**Data sovereignty and governance**

All activities of the SMArtCARE initiative are performed under the supervision of a steering body of neurologists, neuropaediatricians, and patient representatives. The registry is managed by the University Hospital Freiburg and cooperation agreements have been signed with the more than 50 participating treatment centres. The centres receive a case-specific remuneration for their documentation effort. Participating centres can use their own data for scientific purposes at their sole discretion. Data analyses across centres and publications of several centres may only be performed after prior approval of the steering body. Consequently, SMArtCARE understands itself as a research network in which the participating centres can address new research questions and suggest data analyses.

At present, SMArtCARE needs financial support by the pharmaceutical industry. However, the contract stipulates that the registry is in complete control over both the analysis and the publication of the data. A detailed statistical analysis plan is currently under development and will be finalised prior to the first database lock.

**Further development and benefit of the SMArtCARE initiative**

Until now, nusinersen is the only one pharmaceutical that has been approved for the treatment of SMA. However, with the approval of further pharmaceuticals the database will be extended accordingly. Other plans include the implementation of a patient portal where patients or their legal guardians, respectively, can log-into to access their personal data and enter Patient Reported Outcomes (PROs) directly to avoid extra work for the treatment centres.

International collaboration is essential to get a sufficient number of patients for certain research questions and subpopulations. In this context, other countries have already expressed their interest in using the SMArtCARE platform. Thus, standardised data exchange must be facilitated for countries that have already established their own databases.

It remains to be seen to what extent SMArtCARE results will play a role in future benefit assessments of new pharmaceuticals for the treatment of SMA and how collaborati-

on between authorities, pharmaceutical companies and the academic network will be organised. On the basis of REQueST – a questionnaire developed by the EUnetHTA (European Network for Health Technology Assessment, www.eunethta.eu) for the self-assessment of registries – SMArtCARE fulfils the essential quality criteria. This useful but quite new principle of a disease-specific database involving various pharmaceutical companies entails a number of challenges in the actual implementation.

In conclusion, the SMArtCARE initiative provides good framework conditions for the generation of further evidence on the long-term efficacy and safety of different therapeutic approaches for the treatment of SMA. Thus, the anticipated results can probably make a major contribution to sound treatment decisions in future – for the benefit of all patients.

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# Status and potential of registry research in Germany

**Professor Andrew John Ullmann | Member of the German Bundestag**

*There are patient-related registries for many different diseases in Germany. The further promotion and design of high-quality registry concepts is an important task for the future for the benefit of optimised social healthcare. Registry studies can be a valuable treatment-related addition to RCT data. Moreover, registry data have the potential to close evidence gaps where RCTs fail. There are various methods for the structured assessment of evidence, e.g. the GRADE method or the more clinically oriented method of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) that is based on a clear definition of the so-called „unmet medical need". Certain quality standards must be observed in the design of registries. Interesting possibilities arise for registries within the scope of digitalisation. High-quality registries become more and more important in view of the best possible treatment of patients.*

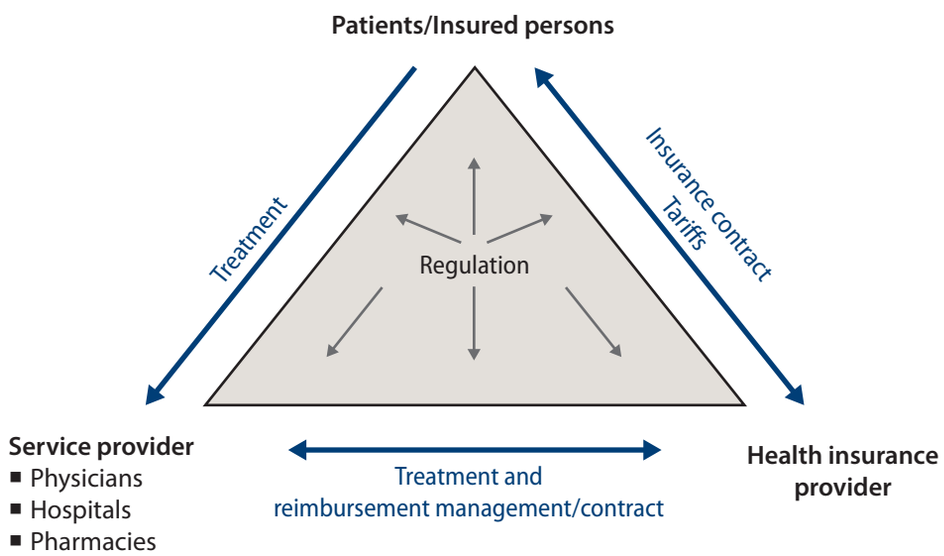
In Germany, the advancement of high-quality healthcare for all citizens and assurance of suitable framework conditions for medical innovations and their affordability are key health policy task (see figure 1). The increasing digitalization and networking in healthcare play a key role. Essential sources of information include the determination, collection and analysis of patient data. Yet the health care sector will have to face significant data protection challenges.

Patient-related registries are especially suitable to analyse the healthcare system under routine conditions and outline potential opportunities for improvement. They can demonstrate what influence various routine care services have on the course of the disease and the patients' quality of life. Moreover, they can provide information about the quality of the treatment in various institutions and care sectors. Thus, registries offer a huge potential for a high-quality healthcare.

Although there is no central national cancer registry in Germany at present, there are a variety of disease or treatment-specific registries, respectively, at regional and national level. The best known registries are probably the so-called cancer registries that are under the responsibility of the federal states and not only received uniform specifications at national level, but also sustained funding by the health insurance providers with the Cancer Screening and Registry Act in spring 2013 that was adopted under the leadership of the former Federal Health Minister Daniel Bahr.[1]

In the past, registry concepts have also been developed for rare diseases and cardiac diseases. Examples of existing national disease registries include the German Paediatric Cancer Registry, German Registry for Stem Cell Transplants (DRST), German Reanimation Registry, DIVI-Registry Healthcare Research Intensive Care Medicine, Substitution

## Further development of high-quality healthcare




Source: own research

Figure 1: Regulatory efforts for a high-quality healthcare must take both the framework conditions for medical innovations and their affordability into consideration.

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Registry, German Endoprosthesis Registry, German Registry for the Long-term Observation of Therapy with Biologics, Biosimilars and Januskinase (JAK)-Inhibitors in Adult Patients and Patients with Rheumatoid Arthritis (RABBIT), and the Registry for the Long-term Observation of Patients with Axial Spondyloarthritis (axSpA) or Psoriasis Arthritis (PsA) (Rabbit-Spa).

However, there are considerations and specific requests for the establishment of registries for a variety of case scenarios, such as for emergency care. The German Diabetes Association (DDG) is currently also engaged in setting up a national diabetes registry to pool the activities of existing decentralised diabetes registries.

Supporting the development and further development of patient-related registries that shall and must meet high quality standards will promote research and treatment research and thus be of benefit for the whole society that significantly takes advantage of medical progress.

The corresponding initiatives at European level should also be taken in consideration. Especially in case of very rare diseases, the network and coordination of registry dates across Europe provides a tremendous potential.[2,3]

**Evidence-based medicine and registry data**

There are – partly very controversial – discussions over and over again about the value of registry data for the approval of therapies or evaluation of their benefit according to the principles of evidence-based medicine. Randomised controlled studies (RCTs) are often considered the gold standard in the evaluation of the benefit risk ratio in the approval process and during Health Technology Assessments (HTA), like our benefit assessment procedure of the Federal Joint Committee.

There are, however, certain constellations in which it is not possible or appropriate to conduct a RCT from a methodological or ethical point of view. This might be the case in special therapy situations, if e.g. a disease is very rare, if vulnerable patient groups are affected, or in case of a high medical need with a lack of therapy alternatives.

## Criteria, evidence base and additional considerations that impact the strength and direction of the GRADE recommendation

1. Problem: Is the problem a priority?
2. Desirable effects: How substantial are the desirable anticipated effects?
3. Undesirable effects: How substantial are the undesirable anticipated effects?
4. Certainty of evidence: What is the overall certainty of the evidence of effects?
5. Values: Is there important uncertainty about or variability in how much people value the main outcomes?
6. Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?
7. Required resources: How large are the resource requirements (costs)?
8. Certainty of evidence of required resources: What is the certainty of the evidence of resource requirements (costs)?
9. Cost effectiveness: Does the cost-effectiveness of the intervention favour the intervention or the comparison?
10. Equity: What would be the impact on health equity?
11. Acceptability: Is the intervention acceptable to key stakeholders?
12. Feasibility: Is the intervention feasible to implement?

Source: GRADE EtD framework

Figure 2: The available evidence and type of intervention are major criteria of the GRADE method.

These specific situations often require customised procedures . With increasing individualisation of medical therapies, especially in the field of pharmacotherapy, these constellations will appear more frequently.

Registry studies can not only provide a valuable addition to RCTs, they also have the potential to close evidence gaps where RCTs fail. From the patients' perspective, these can contribute to their having a faster access to treatment innovations. A precondition for this is not only that registry studies are conducted properly in terms of methodology, but both validity and quality of the underlying data are essential, like in any other study.

The value of registry data for the approval and benefit assessment of therapies thus depends on their validity and quality. There are several methods for a structured assessment of evidence. The GRADE method evaluates existing subject or discipline-specific scientific publications, respectively, and issues ratings independent of the addressed question (see figure 2).[4] The classification of the clinical benefit is performed on the evaluation and respective grouping of existing scientific publications. This results in the recommendation. Thus, the level of recommendation depends on the evidence and intervention.

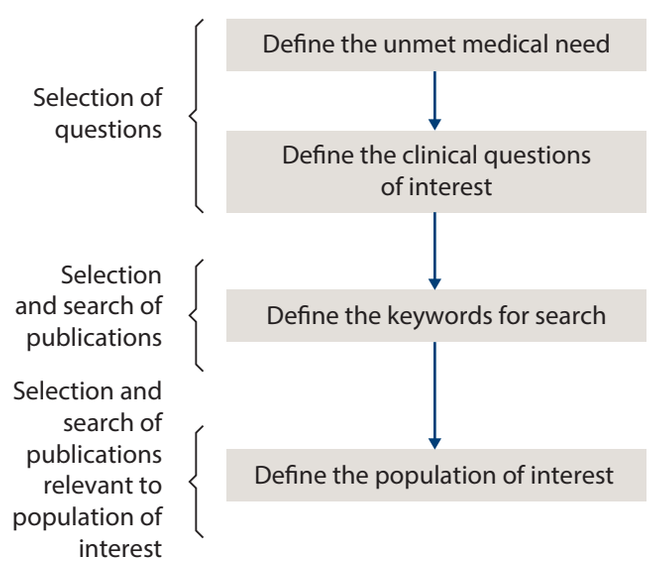
In contrast, the ESCMID method is more clinically oriented (see figures 3a and 3b).[5,6] The level of recommendation does not depend directly on the quality of evidence of the underlying scientific publications, e.g. not on the number of scientific publications based on RCTs. It rather depends on the specific research question and thus allows more differentiated statements. The ESCMID method makes it easier to identify treatment gaps, i.e. the unmet medical need, that have not yet been sufficiently taken into account in the provisions for benefit assessment in the SGB V and the Ordinance on the Benefit Assessment of Pharmaceuticals (AMNutzen-V).

**Quality standards and perspectives for registry data**

In order to determine the value of registries, formal and contextual quality standards must be taken into consideration (see figures 4a and 4b). Therefore, registries must define a clear objective and benefit. It should be clear from the outset for which purpose data are collected in a registry, in particular to ensure validity and quality of data.

Registries should differ significantly with regard to their tasks and objectives. It is essential for their acceptance that a direct of indirect benefit can be derived from data analysis for service providers or third parties. The need for the establishment of a registry in a specific subject area must be determined and also why there is no alternative, e.g. in

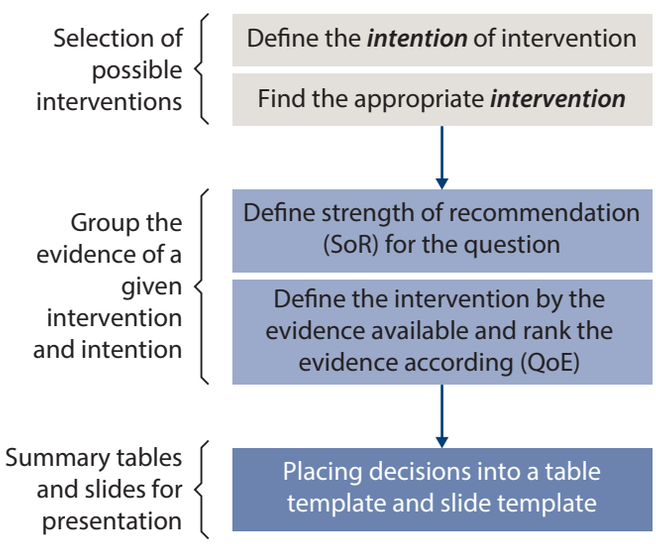
**ESCMID Guideline Algorithm (I)**




Source: European Society of Clinical Microbiology and Infectious Diseases

Figure 3a: The ESCMID method uses the treatment demand as the starting point for all considerations.

## ESCMID Guideline Algorithm (II)




Source: European Society of Clinical Microbiology and Infectious Diseases

Figure 3b: The ESCMID algorithm is more clinically oriented and does not rely on the quality of the evidence alone.

form of a study. Moreover, the focus should usually not be placed on a specific product. Registries should ensure transparency regarding financing and potential conflicts of interest. Irrespective of the quality and validity of the data, transparency can be paramount, if registries shall e.g. be used for the benefit assessment of novel therapeutic approaches.

In addition, data protection aspects of registries must be specified from the outset. All involved patients should always know by whom and for what purpose their data are collected and used. At the same time, registries should rely on the highest technical data security level at all times to create and maintain confidence.

## Requirements for registries (I)

- Different in terms of **objectives** and **tasks**
- Data analysis of a registry must provide a direct or at least an indirect **benefit** for service providers or other third parties
- **Need** of a certain subject area and why there are no alternative solutions (e.g. studies), for example indication quality

Source: own research

Figure 4a: The benefit of data analysis for physicians is essential for the acceptance of registries.

## Requirements for registries (II)

- **Conflicts of interest:** Auftraggeber eines Registers (z.B. Behörde, Leistungserbringer, NGO oder Fachgesellschaft)
- Plausible and transparent **financing**
- Team of clinical **experts**
- **Technical expertise:** Design, logistics, quality, and data security
- **Professional expertise:** Data analysis and interpretation

Source: own research

Figure 4b: Transparency, data protection, clinical and methodological expertise are key requisites.

Expert clinical knowledge and high-level methodological expertise are essential for the establishment and operation of registries. This is the only way to ensure both validity and quality of data and their usability for HTA. Furthermore, professional expertise is also essential for the analysis and interpretation of registry data. With reference to the „fair comparison“ during benefit assessment – as

requested by the IQWIG[7] – it should be noted that other methodological instruments are available for this comparison than in treatment-related research in the early stages of clinical research. Moreover, evidence from high-quality registries plays an equally important role during benefit assessment and quality-secured application in clinical practice, especially in situations, in which RCTs cannot be conducted or only on a limited basis, e.g. due to the rareness of a certain disease.[8]

In view of the increasing digitalisation, aspects of the design, data logistics, usability for AI as well as the aspect of data security that must not be neglected, technical expertise is also paramount. Registries are usually designed for the long-term. Therefore, long-term financing should also be ensured in the planning phase.

Registries that have been designed in this way will provide an added value and ensure that patients have access to advanced, innovative therapies in times of individualised medicine and close treatment gaps. After all, the ultimate goal is to achieve the best possible treatment of patients.

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# Unclear regulatory requirements represent an obstacle for registries in Germany

**Dr Florian Staeck**

With an increasing level of high-precision therapy, new framework conditions emerge for evidence generation in medicine. Traditional „gold standards" such as randomised clinical studies (RCT) can no longer be used in all situations.

But it remains to be seen whether data generated in registries can supplement or even replace RCTs in the context of early benefit assessment in such a way that their results are relevant for an additional benefit. Therefore, much will now depend on whether established or future registry operators will be able to generate high-quality comparative data. The participants of the 10th meeting of the „Interdisciplinary Platform on Benefit Assessment" in Fulda on 18/19 October 2019 under the title „Good registry practice – What are the (additional) benefits of registry data?" were convinced about that.

**No registry for registries so far in Germany**

In addition, data were recorded in registries that have already been collected elsewhere. Participants explained that it was difficult to speak of „registry data" due to certain definitional ambiguities. So far, there was no current overview in terms of a registry of registries in Germany. However, it can be assumed that there are more than 1,000 structured data collection that can be referred to as a registry in a broad sense. Participants stated that a study commissioned by the Federal Ministry of Health could clarify the situation in 2021. The legal basis for registries also varied: Some of them – like the cancer registry or lately the implant registry – had a legal basis and were associated with a notification obligation. And others were merely based on the data donor's informed consent. A third group like the heart attack registry Berlin-Brandenburg used an exemption to record data for research purposes.

Participants noted that the discussion was currently accompanied by an unsubstantiated level of euphoria. This development bore chances but also risks and problems. It was therefore necessary to bundle these efforts in order to collect high-quality data while avoiding a waste of resources. In their debate, participants stated that the latter was currently taking place to a considerable degree. Attracted by funding, registries were established for which it was highly questionable whether they could be operated in a qualitative and financially sustainable manner. Moreover, generalisation of the data generated in registries might be restricted due to regional focus or other limitations.

One major reason for this challenge were different goals and needs of scientists at universities on the one side and pharmaceutical companies on the other side as to which data should be collected and which research questions should be addressed with a registry. In the bilateral discourse between regulatory authorities and research-based pharmaceutical companies, mainly product-related registries had been established so far. Manufacturers would take care of data collection and monitoring themselves on the basis of contracts they had concluded with clinicians. Meanwhile, several participants were convinced that disease-related registries had a larger knowledge potential so that it would make more sense that pharmaceutical companies join existing registries.

However, state-funded registries also had significant structural deficiencies that would preclude their reasonable use within the scope of early benefit assessment. Regional, poorly interconnected registries with inconsistent data access and only partially consistent data sets limit the use e.g. of cancer registries for benefit assessment.

Besides state registries, parallel small-scale new registries had been established that were sometimes even initi-

ated through the innovation fund; the Federal Joint Committee (G-BA) played a major role in this process. So far, due to a time-limitation within the scope of early benefit assessment, manufacturers had been obliged to operate a registry in five cases – but participants reported that there had not been any reevaluations after submission of analysis data so far.

**Preselection of registries by the G-BA**

It was controversially discussed whether the G-BA should preselect registries via its recommendations for pharmaceutical companies. Other participants replied that such a recommendation practice by the G-BA did not appear feasible solely with a view to financial interests that may be involved. This was contradicted by the argument that the important structure formation of the German „registry landscape" should not be slowed down by „small-scale" competitive proof points. For example, the G-BA could complements its recommendation practice by commissioning the German Institute for Quality Assurance and Transparency in Healthcare (IQTiG) which would then be responsible to establish criteria for a sound preselection of registries.

Other participants requested that in addition to the traditional RCTs, other methods for the evaluation of comparative evidence must be developed. They argued that the advantages of an increased high-precision pharmacological therapy also required new methods of comparative evidence generation.

During the discussion, the participants expressed different levels of optimism about the significance and potential benefit of data that have been recorded in registries or specifically dedicated for this purpose. One group advocated the idea, as real-life treatment processes could be reflected with registries – contrary to those by clinical approval studies. Insofar, registries would be an example for contextual thinking deviating from point-specific treatment considerations.

They also argued that there was no other option than to include these patients into registries and observe the treatment processes in case of extremely expensive gene therapies or very rare diseases. An improved networking at European level was also mentioned as an option to increase both scope and significance of registries.

The US American sentinel initiative started in 2008 was mentioned as an example to demonstrate the potential of such an approach. Part of this monitoring programme would have been to establish registries from routine data of health insurance providers. In this way, some major health care issues were already resolved.

Other participants evaluated the quality of the data from registries more cautiously. It could not be discussed abstractly, as it depended on the respective research question. It would also be important to note that benefit statements could only be made in direct comparison. And comparisons could only be fair if they were based on equal starting conditions.

This would not necessarily be a plea for randomisation – if this structural equality could also reliably be established by other means. They explained that demands on fairness would be all the higher, the smaller the expected differences e.g. between two substances was. Against this background, interpretations of small effects within the scope of registries were supposed to be quite challenging. They outlined that hopes that a registry would be less complex and thus less expensive than a randomised controlled study could hardly be fulfilled. For the required data quality would be the expensive component – both in RCTs and registries.

**Application of the PICO process is mandatory**

When it comes to the analysis of data from registries for the purpose of benefit assessment, application of the PICO elements (Patient population, Intervention, Comparison, Outcome) in the required quality was an indispensable prerequisite. This would also apply for genetic characteristics – but e.g. in five or ten year old historic controls they question would arise as to whether such data are even available. In general, the missing randomisation in case of registries makes dealing with confounders difficult.

Participants summed up that a registry could also provide important information for questions of benefit assessment. However, the crux of the matter would often be the quality of the data. The paediatric registry of the Association for Paediatric Oncology and Haematology (GPOH) shows how challenging the structural requirements are for the collection of high-quality data over a long period.

Due to the rareness of the diseases, the best available evidence would generally not be reflected by an RCT. Activities of the GPOH study groups comprise the conduction of a series of consecutive therapy optimisation studies. Participants reported that these studies were characterised by continuous and population-oriented recruiting, uniform documentation, as well as plausibility checks and mandatory data synchronisation of the cases with the paediatric registry.

They said that only such a sophisticated research infrastructure and continuous monitoring ensured a high data quality which is required for reliable analyses over several decades. The participants also underlined that it was extremely helpful for the work of paediatric oncologists that the G-BA had defined certain requirements for centres in paediatric haemato-oncological treatment in 2007, including an obligation for diagnostic backup through reference laboratories. Such a structure formation based on the specifications of the G-BA could not be observed in many other specialist groups.

However, participants recalled that such a stable registry infrastructure could not only be attributed to the formative influence of the G-BA agreement for paediatric oncology. An excellent cooperative cohesion of paediatric oncologists goes back to the influential collaboration of the heads of three centres who had established this structure since the 1970s – partly against great resistance.

Participants who have been involved in medical politics for many years expressed their doubt as to whether the stringent approach based on binding cooperation of paediatric oncologists could be transferred to other specialist groups; for this flagship project of paediatric oncology was rarely copied by other specialist groups.

The example of SMArtCARE registry for patients with spinal muscular atrophy (SMA) demonstrated that registries are always associated with regulatory and financial challenges. Participants noted that the evidence available at the time of approval was rather limited in most cases. Placebo controlled studies would be methodologically challenging especially in SMA type 3 patients. Against this background, the systematic collection of long-term historical data on the efficacy and safety was essential even after approval. The objective of such data collection was to establish a database and research network for all treatment centres and all SMA patients.

Although 60 centres in Germany, Austria and Switzerland had confirmed their participation in SMArtCARE, so far only 13 centres were certified for data input. Participants outlined that this was mainly attributable to delays in the approvals of the ethics committees, as interventional studies were still given priority. Moreover, there were various obstacles for a sustainable financing of registries. Therefore, the challenge was how the participating centres

could be provided with the required resources for the documentation of follow-up data – ideally over several years. However, they have not yet found satisfactory answers for this issue.

**Disease burden is reflected realistically**

Other participants presented the example of a multiple sclerosis registry that had been initiated by a network of physicians. They said that the respective data set that had been drawn up for almost 10 years and was based on the treatment of 25,000 MS patients across Germany showed the potential of registries. These data allowed an observation of the actual treatment situation under the structural framework conditions of the German healthcare system. The disease burden was reflected realistically so that treatment data could be used prospectively as active comparators to clinical studies, if the methodology was further improved. They further explained that the well-structured work of neurologists in private practices would finally enable a targeted treatment advancement.

Several participants outlined that the challenge of sustainable funding of registries remained regardless how encouraging some registry projects might be. Many of them only „survived" as long as funding by sponsors is secured. However, if the industry funded a registry, its independence might become an issue e.g. if sponsors requested to get access to the raw data.

The required longevity of registry poses specific challenges for potential operators in the industry and at hospitals. It was not enough to establish a registry on the day the G-BA requested the collection of data. Instead, this would have to be initiated a few years earlier, ideally during the first consultations between manufacturer and regulatory authority. Especially in rare diseases, the goal would have to be to start data collection at the earliest possible stage.

Sporadically, national governments – e.g. in the Netherlands – deal with the question of how registries could be financed by the state on a long-term basis. In Germany, six selected registries were currently supported with 16 million Euros over several years within the scope of a funding initiative of the Federal Ministry of Research (BMBF). Nevertheless, this initiative would not be able to solve the funding needs of many registries on a permanent basis.

A precise contract design became increasingly important as more partners would (have to) be involved in the financing of registries. According to the participants, one trend that was not only observed in the USA is hardly convincing, i.e. commercial stakeholders engaging as operators of registries and subsequently selling data to pharmaceutical companies to refinance their investment.

Some participants emphasised that despite a positive attitude towards registries it was difficult to predict future perspectives. This applied in particular to the electronic patient file (ePA) that should be provided to all people with statutory health insurance as of 2021. Even according to optimistic assumptions, the ePA should achieve a level in future making it possible to partly or fully replace or complement the task of a registry. Against this background, the development of registries was currently characterised by a considerable level of dynamics. This applied especially for the question as to whether data should be stored decentrally on a permanent basis and only pooled for analytic purposes.

**Quality assurance still in a state of flux**

During the debate it became apparent that open regulatory issues will be decisive for the future of registries. Thus, registry operators were uncertain as to which quality assurance strategy they should pursue to increase the significance of registries. Similar questions arose regarding the

duration of registries and number of patients to be included. Participants noted that it should be considered that registries that do not fully include subjects would be associated with a high risk of bias for methodological reasons.

Moreover, a clearer picture will emerge about the practice of post-market surveillance that the G-BA can now impose on pharmaceutical companies after reorganisation by means of the Act for Greater Safety in the Pharmaceutical Supply System (GSAV) depending on how the G-BA will in fact impose these conditions in practice. Such data collections for the purpose of benefit assessment could be requested by the G-BA in case of conditional marketing authorisation, marketing authorisation under exceptional circumstances, or orphan drugs.

With the GSAV, politics expressed the hope that results from RCTs and registries should complement each other in order to create an evidence level for pharmaceuticals e.g. with conditional marketing authorisation within the scope of post-market surveillance enabling benefit assessment with a quantifiable additional benefit. However, the future status of registries in this process has not yet been demarcated.

## DISCUSSANTS

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# What are the (additional) benefits of registry data?

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