# How to Overcome Scientific Standstill for Very Rare Diseases: Clinical Trials or Clinical Registries?

## Wie kann der wissenschaftliche Stillstand bei der Erforschung sehr seltener Erkrankungen überwunden werden: Klinische Studien versus Klinische Register?

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## Background

In 2001 the EU directive 2001/20/EG for Good clinical practice (GCP) has been adopted and in 2004 in Germany implemented by the 12th amendment of the German drug law [16]. This amendment intended to increase patients' safety by randomized clinical trials investigating risk and efficacy of new drugs or drug combinations compared to established standards under the strict regulations of Good clinical practice (GCP). However, these regulation did not only apply to trials sponsored by pharmaceutical companies, but also for those trials initiated by clinical researchers causing many problems to find adequate financial resources to conduct these studies [13]. Although, the EU directive 2005/28/EG and the 14th amendment of the German drug law included some of the researcher`s concerns there still many remain many unsolved problems [6].

Especially for children and adolescents with cancer there is still a serious problem to conduct trial since many of these entities are very rare and even multinational studies do not reach case number that allow adequately powered randomized clinical trials. Before the 12th amendment these patients could be treated according to expert opinions and data were collected in clinical registries, so-called treatment optimization studies. The scientific progress of treatment regimen was made possible by historical comparison of prospectively documented patient data [14]. Since this is now prohibited by law we are facing a scientific standstill preventing further improvement of treatment for these patients.

## Risk adapted treatment in cancer patients

Today, there is a trend to treat patients with cancer according to the individual relapse risk. In patients with excellent prognosis, treatment intensity will be reduced to avoid acute and long-term toxicity as much as possible, while treatment is intensified in high risk patients to increase cure rates. Since overtreatment as well as undertreatment could be life threatening risk adapted therapy has to be investigated prospectively in different subgroups of one disease. An excellent example to demonstrate the problems for such investigations in very rare disease is the treatment for patients with lymphocyte predominant Hodgkin Lymphoma (NLPHL).

## The ambiguous biology of nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL) – consequences for treatment

NLPHL accounts for about 5% of all patients with Hodgkin lymphoma (HL) [10], the remaining cases are classified as classical HL (cHL) with nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted type as subtypes. Subtyping in cHL has not yet been used for treatment stratification.

More than 60% of patients with NLPHL compared to about 22% of patients with cHL are diagnosed in early favorable stages [10] indicating a low tendency for dissemination in this disease compared to cHL. In addition, the prognosis of patients in stage IA is very excellent and therefore in adults radiotherapy without chemotherapy is recommended [9], while in children and adolescents with stage IA NLPHL no further treatment is recommended after complete resection to avoid treatment related long-term sequele [6,8].

In contrast to patients with cHL or early stages of NLPHL, patients with advanced LPHL tend to transform into NHL [1,2]. Thus, advanced stage NLPHL might be a distinct disease entity closer to NHL than to cHL. In addition, expression of the Glucose transporter-1 is lower in these lymphomas compared to cHL [5], which might be important for FDG-PET evaluation to judge treatment response after chemotherapy. However, patients with advanced NLPHL are still treated according to protocols for cHL patients, although this might not be the best treatment option and there is only one small trial using a NHL-based regimen [3]. Thus, randomized trials to investigate the efficacy of NHL-based treatment vs. standard treatment for cHL are desired to optimize treatment, but they are not possible due to the very low patient number. The German Hodgkin study group reported only 82 patients with advanced NLPHL out of more than 7000 HL patients treated in their protocols over a 15 year period [10]. Then again, there will be no sufficient funding for non-randomized trials and the classical treatment optimization study as a good alternative is now prohibited by law.

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## Epidemiological registries – Possibilities and limitations for treatment optimization

During the past 20 years ESPED (Surveillance Unit for Rare Paediatric Disorders) collected in an anonymized fashion diagnostic and treatment data of patients with rare diseases and severe course of the disease aiming at establishing a fundament for future evidence based diagnostics and treatment recommendation. Important insights in diagnostic and treatment approaches for various very rare diseases such as pseudotumor cerebri, hypersensitivity pneumonitis or childhood multiple sclerosis have recently been documented by ESPED [4,11,15] However, with these registries experiences of individual treatments for these patients' are bundled and it may take a long-time to reach an evidenced based treatment recommendation. Thus, a systematic treatment optimization including quality control instruments [7] as it was possible before the 12th amendment of the German drug law is not provided.

## Conclusions

Progress in treatment guidelines for rare cancer entities cannot be established with RCT'S since the numbers are two small even if international cooperation is achieved. For these cancer entities in children and adolescents register based studies with expert opinion driven amendments of guidelines and comparison with historical register controls should not be prohibited but encouraged. Any attempt should be made to maximize the power of these studies by such as International cooperation and inclusion of young adults, if the biology of disease in young adults is the same as in children and adolescents [12]. If these efforts allow to recruite enough patients for sufficiently powered RCT's these should be encouraged. If the patient numbers are still too small, register based studies including evidence and expert based treatment recommendations using only drugs with EU market authorization and historical controls should be possible.

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