Publishable Summary

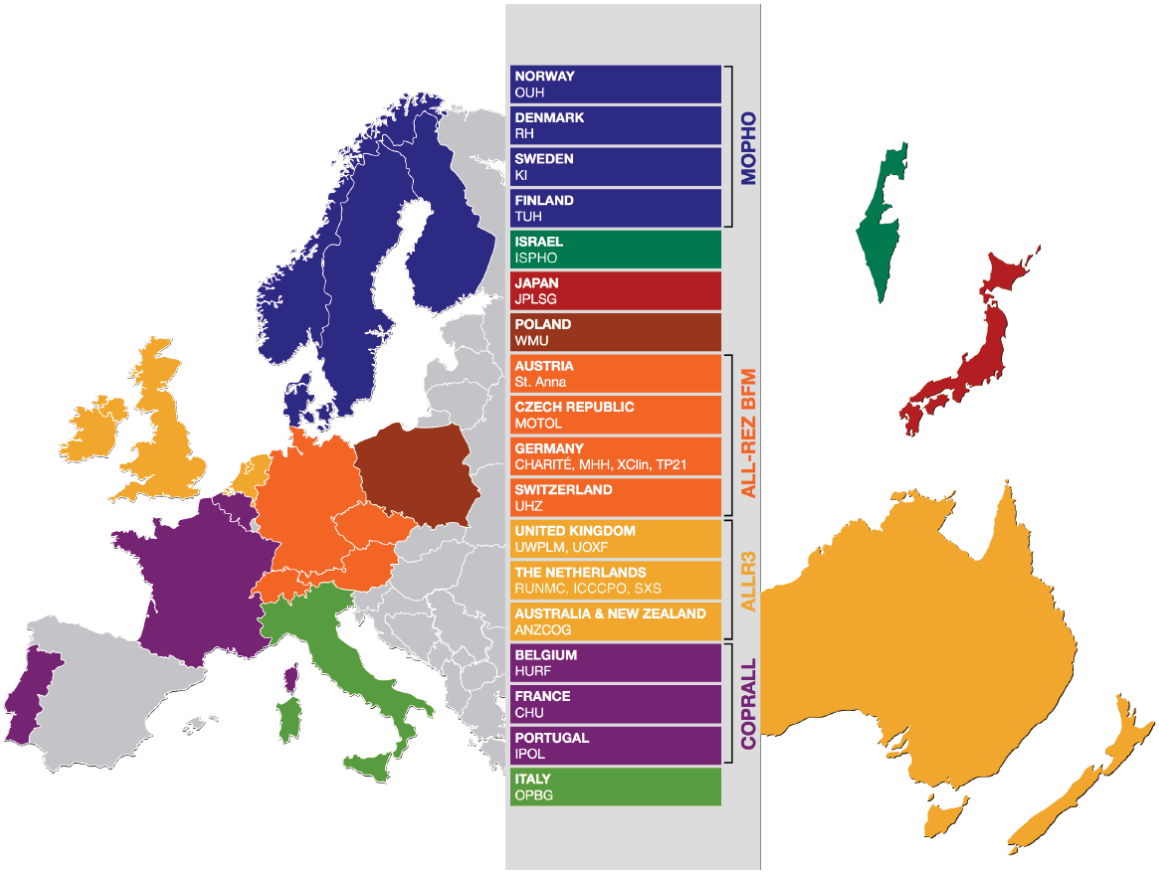
A summary description of project context and objectives

Acute lymphoblastic leukaemia (ALL) is the most common malignant disease of childhood with an incidence of 4/100.000 children per year in Europe. Over the past 4 decades, survival has improved from less than 20% to over 80%. This is primarily the result of risk stratification and intensification of standard therapy for all categories of patients. As a result treatment is complex, prolonged and toxic. About 15-20% of patients suffer a relapse of the disease, resulting in an incidence of about 0.7/100.000 children per year in Europe. With the use of intensive combination chemotherapy and hematopoietic stem cell transplantation (HSCT), currently 40-50% of the children with ALL relapse can be cured. Well defined risk factors allow distinguishing between children with acceptable prognosis after chemotherapy alone, and those who can be cured only by additional HSCT. However, a substantial part of patients still relapse after full intensive treatment suggesting that alternative strategies are required. Thus, ALL relapse is one of the most frequent causes of death in childhood malignancies. In the modern era a number of new drugs are available which could be of benefit for children with ALL. Some of these drugs are targeted to specific pathways or molecules and have little or no side effects and carry the promise of decreasing toxicity and improving outcome. Numbers of paediatric patients with relapsed ALL even in the larger member states are too small to perform prospective controlled clinical trials for improving standard therapy and integrating new agents. Therefore, the IntReALL consortium has been founded as a large international collaborative group with the aim to establish a comprehensive platform for diagnostics and treatment of childhood relapsed ALL in Europe and beyond. The initiative was taken by experts from the International BFM Study Group (I-BFM SG), a collaborative expert group for childhood leukaemia and lymphoma in Europe and other continents (Fig. 1).

Main objectives of the IntReALL project are to

1. implement prospective clinical trials for harmonization and optimization of the best available standard therapy and integration and prospective evaluation of the most interesting new agents
2. implement the infrastructure for a large international trial including GCP conform clinical trial management and a GCP conform web-based study data base
3. to establish harmonized diagnostic procedure for relapsed/refractory ALL and a comprehensive harmonized strategy for tissue banking and biologic studies to improve knowledge on the disease, discover new risk factors and potential targets for new drugs
4. establish a strong and effective network with the other international academic organizations dedicated to paediatric oncology, international regulatory authorities and pharmaceutical industry allowing for optimized development of new agents and with parent organizations to warrant a strategy in the best interests of the children with ALL.
5. involve innovative small and medium sized enterprises (SME's) contributing expertise in diagnostic and therapeutic biotechnology, IT, and management to the Consortium.
6. improve awareness of the public and medical professionals on childhood relapsed ALL thus improving recruitment rates for the trial and informing on the effective use of EU budget with direct impact on improvement of the medical care of the European population.

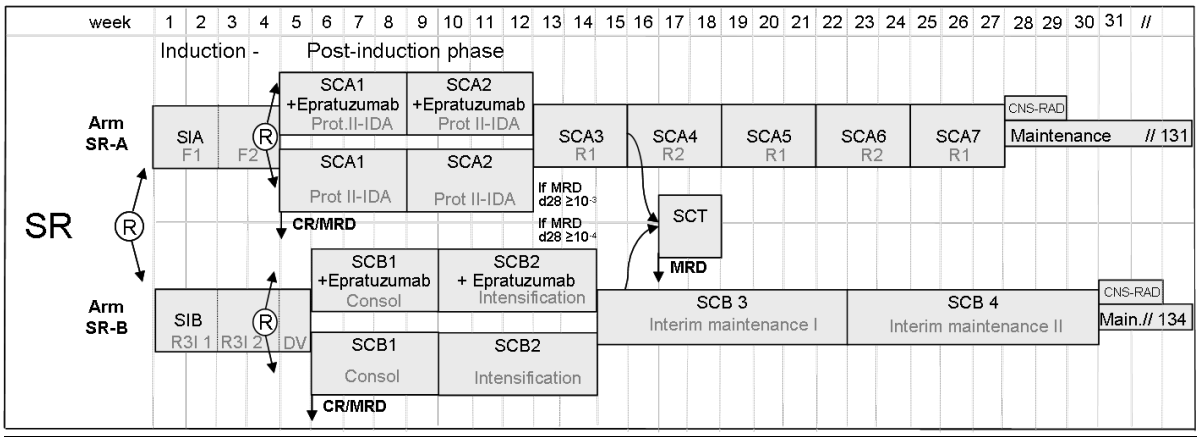
Figure 1: IntReALL Consortium, participating countries and study groups



Description of the work performed since the beginning of the project and the main results achieved so far

In the first 24 month, the basis for the project has been established within 5 work packages, clinical trial, data base and statistics, diagnostics and biological research, networking, dissemination and regulatory affairs, and project management. Separate trials for standard- (SR) and high risk (HR) childhood relapsed acute lymphoblastic leukaemia (ALL) have been developed. For SR patients, the ALL-REZ BFM 2002 and the ALL-R3 regimens are randomly compared to establish the best available standard therapy. Furthermore, as first new and targeted drug, the CD22 directed monoclonal antibody Epratuzumab is randomly investigated during consolidation (Fig. 2). Production, shipment and labelling are warranted by the manufacturer Immunomedics, SME partner of the project.

Figure 2: IntReALL SR 2010 protocol overview



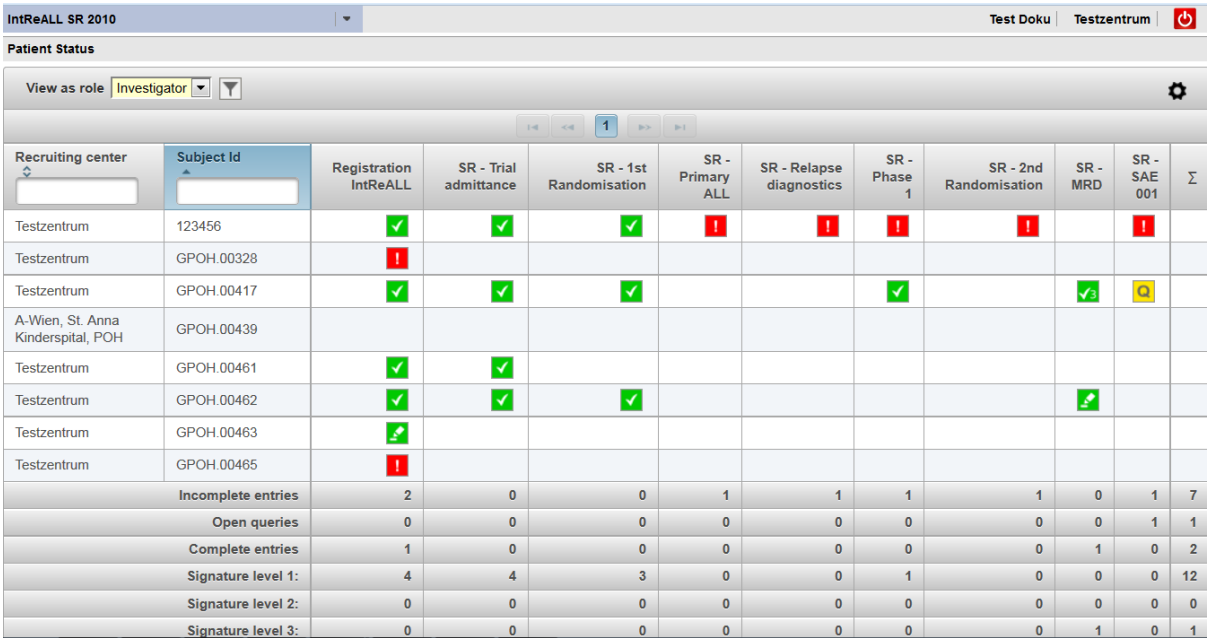
The implementation of the larger SR phase III trial has been prioritized. The trial is fully approved by all required regulatory and ethical instances and has been opened for recruitment in May 2014. A GCP compatible trial infrastructure has been fully established at the international sponsor Charité and the national co-sponsors. The department for legal affairs has set up a framework of contracts covering all involved parties. The finalization of the complex sponsor delegation and site contracts integrating the requirements of the involved pharmaceutical company Immunomedics bound to US law and FDA requirements led to delay of the whole procedure and thus the opening of the SR trial. In the meantime, the majority of participating countries have signed the co-sponsor contracts and have been initiated for start of patient recruitment (Fig. 3). Nearly half of the planned 238 clinical study sites have signed contracts and been opened. A total of 60 patients have been recruited so far showing unexpectedly high randomization compliance.
The central pharmacovigilance revealed a 26 reported serious adverse events.
The Data Safety Monitoring Board (DSMB) has been formed, and started to work according to GCP.
These numbers demonstrate that after solving the demanding organizational, ethical and legal problems there is a high interest in and acceptance of the study among the involved parties and in particular the patients and their families.

Figure 3: Sponsor delegation contracts, initiation of countries and sites, and patient recruitment of the IntReALL SR 2010 trial (status 08.05.2015)

Country	Co-sponsor contract signed	Co-sponsor Initiated	Sites total	Sites Initiated	Patients reruited
Australia / NZ	Yes	10.04.2014	10	7 (70%)	5
Austria	Yes	17.10.2014	8	1 (13%)	0
Belgium	Legal issues		7		
Czech Republic	Legal issues		5		
Denmark	Yes	28.08.2014	4	2 (50%)	1
Finland	Yes	10.10.2014	5	5 (100%)	2
France	Change of site	08.07.2014	30		
Germany	Yes	01.02.2014	57	26 (46%)	11
Ireland	Legal issues		1		
Israel	Yes	14.05.2014	7	4 (57%)	2
Italy	Yes	19.05.2014	27	26 (96%)	34
Japan	Yes	23.10.2014	28	27 (96%)	3
Netherlands	Change of site		6		
Norway	Yes	16.09.2014	5	4 (80%)	0
Poland	No participation				
Portugal	Yes	03.06.2014	3	1 (33%)	2
Sweden	Legal issues		6		
Switzerland	Yes	20.01.2015	9	1 (11%)	0
United Kingdom	Legal issues		20		
Total	11 / 19	11 (58%)	238	104 (44%)	60

A study data base for the SR and the HR trials has been set up using the MARVIN system provided by the SME XClinical. The data base for the SR trial is finalized and has been opened for study data entry since March 2015. XClinical has improved the MARVIN system and adapted it to the requirements of the project, including a multi trial feature.

Figure 4: Patient visit matrix of the MARVIN data base



IntReALL SR 2010 | Test Doku | Testzentrum

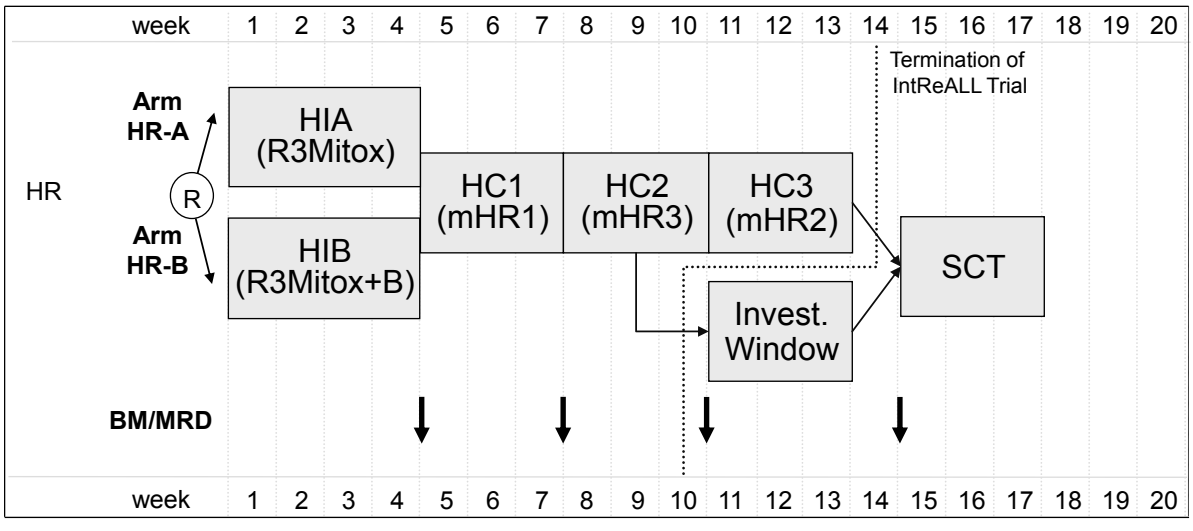
Patient Status

View as role: Investigator

Recruiting center	Subject Id	Registration IntReALL	SR - Trial admittance	SR - 1st Randomisation	SR - Primary ALL	SR - Relapse diagnostics	SR - Phase 1	SR - 2nd Randomisation	SR - MRD	SR - SAE 001	Σ
Testzentrum	123456	✓	✓	✓	!	!	!	!		!	
Testzentrum	GPOH.00328	!									
Testzentrum	GPOH.00417	✓	✓	✓			✓		✓3	Q	
A-Wien, St. Anna Kinderspital, POH	GPOH.00439										
Testzentrum	GPOH.00461	✓	✓								
Testzentrum	GPOH.00462	✓	✓	✓					✓		
Testzentrum	GPOH.00463	✓									
Testzentrum	GPOH.00465	!									
Incomplete entries		2	0	0	1	1	1	1	0	1	7
Open queries		0	0	0	0	0	0	0	0	1	1
Complete entries		1	0	0	0	0	0	0	1	0	2
Signature level 1:		4	4	3	0	0	1	0	0	0	12
Signature level 2:		0	0	0	0	0	0	0	0	0	0
Signature level 3:		0	0	0	0	0	0	0	1	0	1

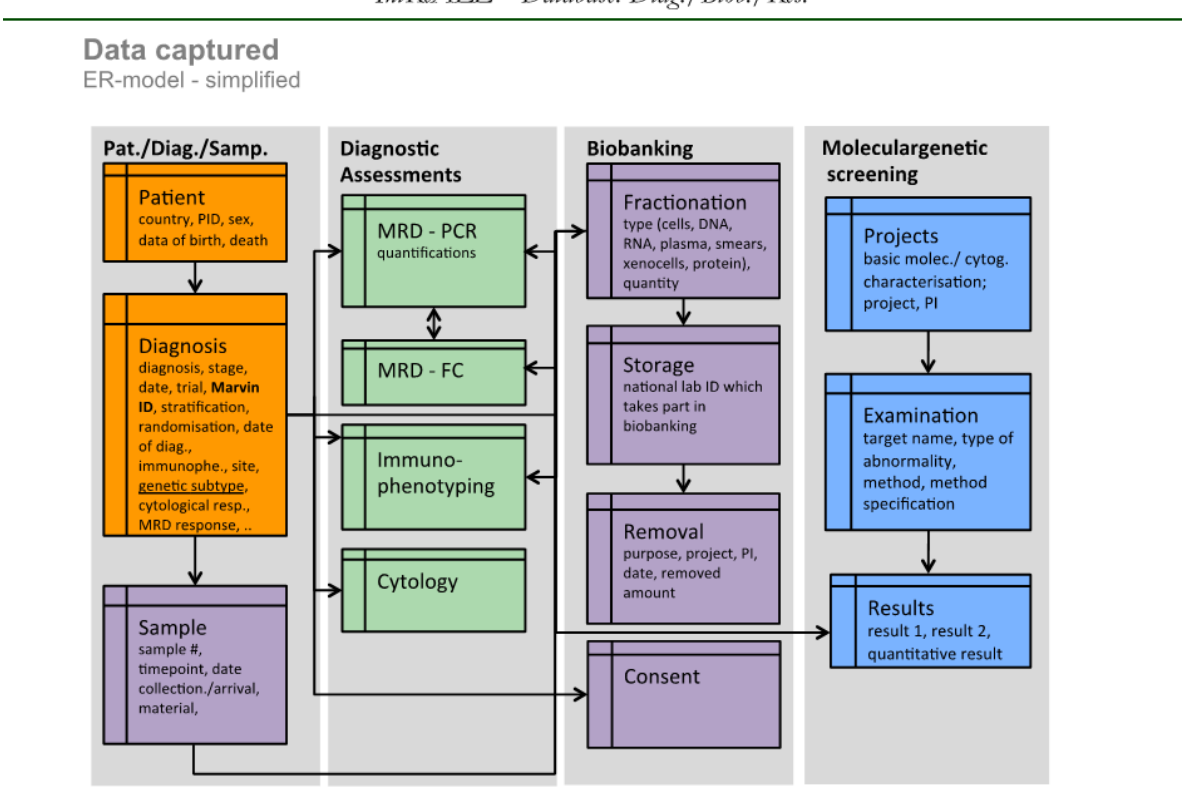
The design of the HR trial investigating the induction regimen Clo/Cyc/Eto had to be modified due to recently reported preliminary adverse data. The Trial Committee (TC) decided to investigate the proteasome inhibitor Bortezomib instead, which had shown an attractive profile in paediatric relapsed ALL. An innovative covariate-adjusted response-adaptive (CARA) randomised design has been developed by the statistics team from Oxford, allowing for early stopping in case of superiority/futility and a flexible randomisation rated based o interim analysis results. The study protocol has been written and agreed by the TC and the involved parties. The study is now submitted to authorities via the voluntary harmonized procedure (VHP) and then further processed using the pathways established with the SR study.

Figure 5: IntReALL HR 2010 protocol overview, new design randomizing ALL-RE3 backbone (R3Mitox) ± Bortezomib (B), modified BFM HR courses (mHR1-3), optional investigational window, stem-cell transplantation (SCT)



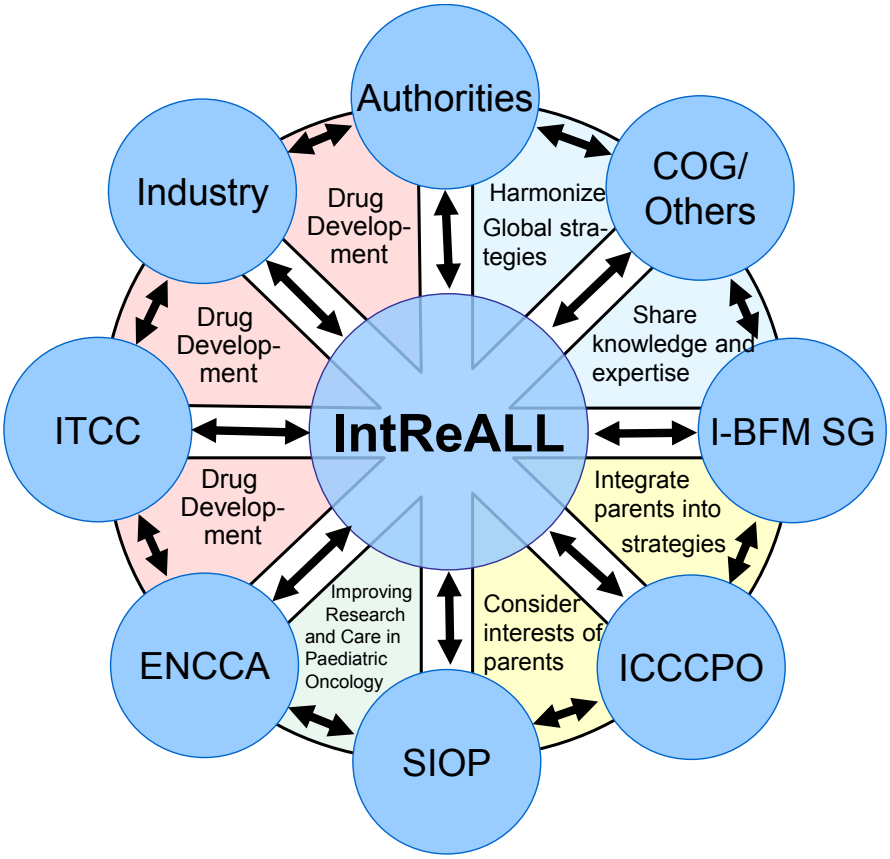
Standardized diagnostic procedures, reference laboratories, and a virtual tissue bank for patient material have been established in all participating countries. A comprehensive strategy for biologic research has been agreed with several projects on pathogenesis of the disease, new risk factors and targets for new drugs. A new company ServiceXS replacing the partner PopGenTech has been selected and is testing candidate genes for genetic screening. An improved genetic classification of childhood relapsed ALL has been established.

Figure 6: Structure of biologic research and flow of research data



A strong network with other relevant academic institutions involved in paediatric oncology and drug development has been implemented including regular and close interaction with the EMA and industry. Several meetings have been held to establish the structure of the Consortium and to discuss the progress of the project. An Ethics Board has developed a strategy to accompany the project. A website and the participation of IntReALL partners in numerous congresses support the awareness on the project in the public and among clinical professionals. A straight forward project management for the project has been established to integrate the specific requirements of an international clinical trial into the framework of a FP7 program.

Figure 7: IntReALL networking structure



Expected final results and their potential impact and use (including the socio-economic impact and the wider societal implications of the project so far)

The IntReALL project is establishing the largest clinical trial for treatment of childhood relapsed ALL in the world. It develops the best available standard treatment strategies as backbone for further European trials within randomised phase III trials in a reasonable time span. The IntReALL trials will serve as a reference for this particular disease for the whole world. Furthermore, the IntReALL Consortium provides a unique platform for drug development in childhood ALL with randomised phase III trials investigating the most promising new agents timely and fulfilling all licensing requirements. With the IntReALL SR 2010 trial, the role of Epratuzumab in childhood relapsed ALL will be determined with direct relevance for licensing of the drug. With this particular trial the Consortium will pave the way for integration of future immune-therapies and other targeted treatment strategies in relapsed and also primary ALL. The investigational window implemented in the IntReALL HR 2010 trial will be used to investigate the efficacy and activity of the bispecific T-cell engaging CD3/19 directed monoclonal antibody Blinatumomab as decisive trial for filing in paediatric indications, sponsored by Amgen, a stream within the HR trial will be established including patients with JAK/STAT pathway inhibition sensitive leukaemias for investigation of theJAK2-inhibitor Ruxolitinib. These new agents provide completely different mechanisms of anti-leukaemic action and may break drug resistance of leukaemias thus contributing to improvement of prognosis of this disease. Furthermore, proven effective targeted agents may replace unspecific and toxic chemotherapy and allow for reducing the burden of acute and long-term side effects for the patients. With IntReALL 2010, a comprehensive infrastructure for the GCP-conform conduction of an international trial is set up which will serve as a platform for consecutive trials which can fully benefit from the established tools. This includes also the optimized web based data system MARVIN which will be available for future projects without repeating the labour-intensive implementation phase. The IntReALL Consortium will serve as reliable partner on drug development in childhood ALL for industry and authorities warranting realistic paediatric investigational plans. The IntReALL Consortium will warrant drug development strategies in the best interest of the patients by integrating the point of view of the parent groups. The strong academic network will warrant drug development strategies in childhood relapsed ALL fully on a medical and scientific basis free from commercial interests. A tissue bank on childhood relapsed ALL samples of unique size and quality will be available for research within the consortium and international collaborations. With gene pooling and next generation sequencing technologies, a unique data set on comprehensive genetic characterization of childhood refractory ALL will be available for association with clinical and outcome data leading to new insights into pathogenetic mechanisms and development of resistance. Such data will also be made available for the scientific community as reference for further research project. The early integration of the ICCCPO as authorized international organization of parents of children with cancer warrants improvement of compliance of the affected families, facilitate the trial processes and will be exemplary for other trials. The broad strategy of public information with a well established public website, presentation of the project and results at public and scientific events and congresses will improve the awareness of the population on the problems of refractory leukaemia in children and the way to find solutions within the European Union. Such information will improve the willingness of the public to transfer competence and budget to centralized European institutions, because a direct benefit for all members is evident. Well-trained and informed clinical, documentary and research staff in Europe and worldwide will give better health care to children with relapsed leukaemia, a disease that was considered to be fatal until recently.