SIXTH FRAMEWORK PROGRAMME

LSH-2002-2.2.0-3

Life Sciences, genomics and biotechnology for health

(LifeSciHealth)

Contract for:

NETWORK OF EXCELLENCE

Annex I – "Description of Work"

Project acronym:	**European LeukemiaNet**
Project full title:	**Strengthen and develop scientific and technological excellence in research and therapy of leukemia (CML, AML, ALL, CLL, MDS, CMPD) by integration of the leading national leukemia networks and their interdisciplinary partner groups in Europe**
Proposal/Contract no.:	**503216**
Related to other Contract no.:	
Date of preparation of Annex I:	**28/07/2004**
Start date of contract:	

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The European LeukemiaNet

With regard to state of the art of networking on leukemia we refer to the report which has just appeared (Hehlmann et al., Leukemia 2004).

1. PROJECT SUMMARY

Leukemias are a challenge to society and a cost factor because of their frequency in all age groups. They also serve as a model for a variety of diseases and possess exemplary relevance for basic research and patient care. Leukemia research and therapy have achieved high standards and even a leading position in several European countries with regard to clinical trials, standardization of diagnostics and molecular studies of signal transduction and gene expression. A true European world leadership, however, has not been accomplished yet due to national fragmentation of leukemia trial groups, diagnostic approaches and treatment research activities and a need for central information and communication structures.

The objective is to integrate the 78 leading leukemia trial groups (CML, AML, ALL, CLL, MDS, CMPD), their 83 interdisciplinary partners (diagnostics, treatment research, registry, guidelines), industry and SMEs across Europe to form a cooperative network for advancements in leukemia-related research and health care. Integration will be supported by central information, communication, education and management structures. Other goals are to intensify target and drug discovery, to shorten the time period to clinical translation, to apply advanced genomics, telematics and biotechnology to therapeutic progress and to promote research relevant also for solid cancers by large clinical trials. Furthermore, metaanalyses of specific subaspects, elaboration of prognostic scores, recognition of gender specific differences, creation of uniform data sets for trials and registration, introduction of standards for diagnostics and treatment and development of evidence based guidelines will be promoted throughout Europe. The proposed network will have the expertise and critical mass for European added value and world leadership. It will structure European research durably, spread European scientific excellence in the field of leukemias and can start immediately.

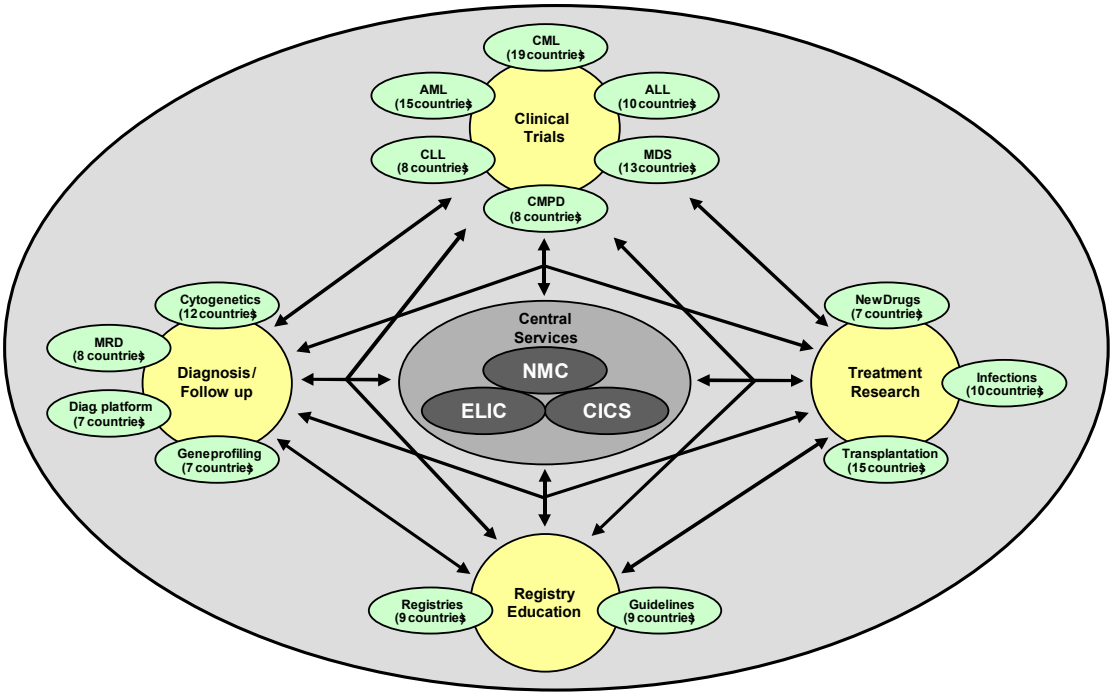

Fig. 1: Network Structure

Fig. 2: Geographic distribution of lead participants and participants representing national study groups comprising more than 1,000 centers in 22 countries

2. PROJECT OBJECTIVES

Rationale: Leukemias are a challenge to society and a cost factor because of their frequency in all age groups. They also serve as a model for a variety of diseases and possess exemplary relevance for basic research and patient care. Leukemia research and therapy have achieved high standards and even a leading position in several European countries with regard to clinical trials, standardization of diagnostics and molecular studies of signal transduction and gene expression. A true European world leadership, however, has not been accomplished yet due to national fragmentation of leukemia trial groups, diagnostic approaches and treatment research activities and a need for central information and communication structures which would allow integration and strengthening leukemia research and therapy across Europe.

The objective of this proposal therefore is the creation of an interwoven network that integrates the leading national trial groups of the various leukemias (AML, ALL, CML, CLL, MDS, CMPD) across Europe and their interdisciplinary partners in diagnostic and treatment research, molecular- and cytogenetics, detection of minimal residual disease, gene profiling, transplantation, supportive care, new targets and new drugs, trial support, prognosis, research etc. and provides central management, information and communication structures for strengthening European research and patient care in the field of leukemia.

The leukemia trial groups shown in Table 1 representing several thousand participating centers and ten thousands of study patients treated within the trial groups form the backbone of the network. The network is complemented by the integration of nine interdisciplinary research and support platforms as shown in Table 2 which provide the support and research expertise required for high quality networking and excellence and represent subnetworks on their own.

The integration and interdisciplinary cooperation brings together 116 participants or approximately 900 researchers from basic science and clinical trials and their funded research programs from 22 countries. They will overcome national fragmentation and will provide the critical mass to achieve research and treatment goals that cannot be achieved by single European countries.

The commitment of approximately 78 national leukemia trial groups and their 83 interdisciplinary partner groups across Europe to European integration and networking provides the critical mass to address the following **objectives**:

1. Establishment of central information and communication structures to create networks and platforms for all leukemias and their interdisciplinary partners. Integration is mediated by exchange of current trial protocols and procedures, information on participating centers and recruited patients and employment of uniform common data sets for comparable study outcomes and evaluations provided by the biometrical center (WP 17). This objective will be achieved through central services: Network Management Center (NMC, WP 1), European Leukemia Information Center (ELIC, WP 2) and Central Information and Communication Services (CICS, WP 3). The central service groups benefit from a three years' experience in similar tasks for the German Competence Network for Acute and Chronic Leukemias funded by the German Ministry for Education and Research (BMBF) and provide the basis for a head start of the network. These groups will also provide training programs, workshops, symposia, exchange of researchers and information programs thereby spreading excellence to health care personnel, researchers and to other countries not yet participating in the network. With the support of NMC (WP 1) the network will be managed in a two layer networking organization. Clinical trial groups for each leukemia and their interdisciplinary partner will form their own European subnet organizations with coordinators, steering groups and management structures. These subnets and platforms will then be integrated in the European Leukemia Network which will conduct the integrated research program detailed below. The network will be managed by the Network Coordinator (NC), the Scientific Network Manager (SNM) and the Steering Committee

(SC) consisting of the coordinators (=Lead participants) of the work packages. The University of Heidelberg will provide the expertise for financial, legal and contractual management.

2. Set up of European networks for each leukemia and related syndrome. These networks as detailed in table 1 will comprise the national trial groups for each leukemia and represent the first stage of networking and European integration.

Table 1: European Leukemia Trial Groups integrated in the NOE

European networks for leukemias and related syndromes	CML	AML	ALL	CLL	MDS	CMPD
Austria	●	●	●	●	●	●
Belgium	●	●		●	●	
Croatia			●			
Czechia	●				●	
Denmark	●	●			●	●
Finland	●				●	
France	●	●●	●	●	●	●
Germany	●	●	●	●	●	●
Ireland	●					
Israel		●				
Italy	●	●	●●	●	●	●
Luxembourg	●	●				
Netherlands	●	●●	●	●	●	
Poland	●	●	●			
Romania	●					
Russia		●				
Spain	●●	●●	●	●	●	●
Sweden	●	●	●	●	●	●
Switzerland	●	●	●		●	
Turkey	●					
UK	●	●	●	●	●	●
European consortia	EI-CML EBMT	EORTC	EORTC	ERIC	EBMT EORTC	ECLAP European ET

3. Set up of European platforms for each interdisciplinary specialty. These platforms as detailed in table 2 are subnetworks of excellence of diagnostic, therapeutic and biometric research groups on their own and constitute interdisciplinary partners enabling the clinical trial groups to achieve the high quality patient care and research required for European leadership.

These leukemia subnetworks and interdisciplinary platforms are integrated to form the European leukemia network. This network will bring together experts across multiple disciplines and institutions to participate, within a formalised infrastructure, in the **rapid discovery and development of cancer therapies**. This initiative will encompass the whole spectrum of drug discovery and development with the ultimate goal of shortening drug development time through a novel alliance among academia, industry, government, and patients. The European Leukemia Network will advance knowledge in all fields of leukemia and will establish Europe as scientific leader in leukemia research and therapy. With improved cooperative structures the critical mass of expertise can be achieved for synergisms in both leukemia research and patient care, by standardising diagnostic procedures (quality assurance),

establishing baseline standard sets for controlled clinical trials, conducting controlled intergroup trials and providing critical patient numbers to study rare subentities.

Table 2: Integrated Interdisciplinary European Research and Support Platforms

Platforms for interdisciplinary specialities	Dia-gnostics	Cyto-genetics	MRD	Gene pro-filing	SCT	Suppor-tive Care, Infec-tions	New Targets, New Drugs	Registry	Guide-lines
Austria		●			●		●		●
Belgium		●	●		●	●			
Croatia					●				
Czechia					●				
Denmark		●	●						
Finland		●		●	●				
France	●	●	●	●	●	●		●	●
Germany	●	●	●	●	●	●	●	●	●
Hungary					●				
Israel						●	●		
Italy	●	●	●		●	●		●	●
Netherlands	●	●	●			●	●	●	●
Poland					●		●		
Spain				●	●	●		●	●
Sweden		●	●	●	●	●	●	●	●
Switzerland	●	●			●	●		●	●
Turkey					●	●			
UK	●	●	●	●	●		●	●	●
European consortia	EGIL			EORTC	EBMT CLWP	EBMT			ESH EHA

4. Performance of clinical trials (all leukemias). Employing uniform common data sets the trial groups will continue their current trials funded by alternative sources (see 10.5. and Table 3) and will start new trials using diagnostic standards established by the diagnostic platforms (WPs 10-13) and employing new drugs provided by pharmaceutical companies and/or the subnetwork on treatment research/new targets/new drugs (WP 16). Criteria for accreditation of trials will be set up.

Table 3: Currently ongoing clinical trials (mostly phase I/II) funded by other sources

CML	Imatinib, other targeted therapies (FLT3, VEGFR), IFNα, ara-C, homoharringtonine, arsenic trioxide, all drugs alone and in combinations, dose ranging, crossover studies, randomized treatment optimization trials.
AML	Induction treatment intensity, G-CSF-priming, autologous transplantation, maintenance, quality of life, subgroup and risk adapted treatment, targeted therapy.
ALL	Risk stratified therapy, MRD-based treatment decisions, evaluation of allogeneic (related/unrelated) SCT, induction treatment intensity, imatinib in Ph/BCR-ABL+ ALL, monoclonal antibodies (e.g. anti-CD20 in B-ALL).
CLL	New agents alone or in combination (purine analogues, alkylating agents), chemoimmunotherapy (rituximab, alemtuzumab), antisense oligonucleotides, erythropoietin, bendamustine.
MDS	Eradication of auto-reactive T cell clones, correction of methylation pattern, intensive therapy with new agents, allogeneic stem cell transplantation.
CMPD	Targeted therapies, imatinib, farnesyl transferase inhibitors, Peg-IFN, thalidomide alone or in combination with hydroxyurea, anagrelide, acetylsalicylacid.

The planned trials are summarized in table 4.

Table 4: Planned clinical trials

CML	• Combinations of targeted therapy with conventional agents (imatinib + PEG-IFN, ara-C, homoharringtonine, farnesyltransferase inhibitors, decitabine, or arsenic trioxide) • New targeted therapies (FLT3 and VEGFR inhibitors) • Risk adapted therapy • Allogeneic stem cell transplantation (SCT) after targeted therapy
AML	• Comparison and validation of treatment alternatives across different trials • New agents targeting mutations of the MLL and FLT3 genes • Treatment optimation evaluating the role of arsenic trioxide in APL • Risk adapted treatment strategies • Integration of SCT into clinical trials
ALL	• Cross-study evaluation of prognostic models • Cooperative development of risk stratified treatment based on MRD • Phase III intergroup studies in rare subtypes of ALL e.g. mature B-ALL • Phase II-III studies with monoclonal antibodies e.g. antiCD20, antiCD52, antiCD22 • Phase II studies with new cytostatic drugs in relapsed/refractory ALL • Phase II studies with imatinib in Ph/BCR-ABL+ ALL • Phase II studies with new molecular drugs • Phase II studies with new cytostatic drugs • Phase II studies with new approaches for stem cell transplantation e.g. dose reduced transplantation, cell therapy
CLL	• Advanced chemo-immunotherapy trials with fludarabine, cyclophosphamide and rituximab or fludarabine + alemtuzumab • Combination with erythropoietin as supportive treatment, relevance of bendamustine • Individualization of therapy according to genotype • Integration of SCT into clinical trials
MDS	• Suppression of early programmed cell death and cytokine dysregulation including angiogenesis dysregulation • Correction of methylation patterns: decitabine, 5-azacytidine • Allogeneic SCT with reduced intensity conditioning programs in comparison with standard conditioning • Trials: Immunesuppressive therapy: ATG, CyA, thalidomide • Phase I/II trials with arsenic trioxide, CD33 conjugates
CMPD	• Study new tyrosine kinase inhibitors, farnesyltransferase inhibitors • Low dose thalidomide and prednisone • Low dose aspirin in low risk polycythemia vera patients • Analysis of non-leukemogenic drugs in comparison to hydroxyurea • Integration of SCT into clinical trials

5. European Registry (all leukemias). A European registry will allow to determine incidence and disease patterns across Europe including gender, age and ethnic differences, investigate familiar aggregations, overlap syndromes or precursor conditions, explore risk factors associations and differences in gene environment interaction, utilizing data from cytogenetic analyses (WP 11) and genomic profiling (WP 13), perform quality of life assessments, recognize subentities on the basis of cytogenetic or gene profiling information, follow-up patients for the development of prognostic scores for old and new therapies and determine proportions of patients in individual countries treated on specific protocols or with specific therapies e.g. SCT (WP 14). The registry will be run by the expert group Biometry for Registry, Epidemiology, Metaanalyses and Prognosis (WP 17). This group has

gained a longstanding broad experience in collecting data, performing metaanalyses and establishing prognostic scores. The data base established by the network will have far reaching implications for research and public health planning far beyond the period of EC-funding.

6. Standardization. Standardized and quality controlled diagnostic procedures and therapies constitute the basis for improvements of clinical outcomes. This concerns all diagnostic approaches such as morphological diagnosis of blood and marrow cells (WP 10), cytogenetics (WP 11), detection of minimal residual disease (WP 12) and gene expression profiling (WP 13) as well as therapies such as transplantation, anti-infection prophylaxis and treatment and the testing of new drugs in phase I/II trials (WP 14-16). The establishment of standards for a wide spectrum of diagnostic and therapeutic applications will raise the quality of research and patient care beyond the period of EC-funding and will predictively have a profound impact on outcome as measured by prolongation of life and cure rates across Europe.

7. Metaanalyses and guidelines. Whenever randomized trials are available for analysis (mostly CML and AML), metaanalyses will be performed and published (WP 17). On the basis of metaanalyses, evidence-based guidelines (WP 18) will be worked out and used for the improvement of patient management and for educational purposes (training programs, workshops in associated countries, exchange of researchers and physicians for training purposes). Metaanalysis will be also performed on combined data sets with rare subtypes of leukemias (WP6).

All objectives can only, or best, be achieved within the proposed network, since interdisciplinary cooperation of leukemia trial groups with diagnostic, therapeutic and biometric research groups is a conditio sine qua non. This proposed integration will create a network with interdependencies of all participants and provide a high quality in research and patient care not achievable outside of the network. It is expected that the improvement of research and the shortening of drug development time will ultimately prolong life and improve cure rates. The benefit will be for patients, their relatives, the researchers and Europe at large. The network structure will accelerate progress and shorten the drug transition time to the application in the patient and ultimately improve leukemia research and patient care across Europe. Based on experience with the German Leukemia Competence Network, the European Leukemia Network will become the world force in leukemia research and treatment.

3. LIST OF PARTICIPANTS AND ASSOCIATED SCIENTISTS

3.1 List of participants

Particip. Role	Partic. Number (n=117)	Participant Name	Participant short name	Country	Date enter project	Date exit project
NMC (WP 1)						
Coordinator	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60
ELIC (WP 2)						
LP	2	Universitätsklinikum Frankfurt	UKF	Germany	1	60
P	3	Universitá Cattolica del Sacro Cuore	UCSC	Italy	1	60
P	4	Deutsche Leukämie und Lymphom-Hilfe e.V.	DLH	Germany	1	60
CICS (WP 3)						
LP	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	6	Medizinische Universität Graz	MUG	Austria	1	60
P	121	Megapharm GmbH	MGP	Germany	1	60
CML (WP4)						
LP	7	Uppsala Universitet	UU	Sweden	1	60
LP	8	Universitá di Bologna- Unita Complessa di Istituti di Cardiologia ed Ematologia	UCCE	Italy	1	60
LP	9	Université de Poitiers	UNPO	France	1	60
LP	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60
P	10	Katholieke Universiteit Leuven	KUL	Belgium	1	60
P	79	Azienda Ospedaliera Ospedale San Martino	OSM	Italy	1	60
P	12	Hospital Clinic Provincial de Barcelona	HCPB	Spain	1	60
P	13	Fundeni Clinical Institute	FCI	Romania	1	60
P	14	Erasmus University Medical Center Rotterdam	EMCR	Netherlands	1	60
P	15	Johannes Gutenberg-Universität Mainz	JOGU	Germany	1	60
P	16	Imperial College London	ICSMT	UK	1	60
P	17	University of Basel/University Hospitals	UNIBAS	Switzerland	1	60
P	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	18	Ankara University	AUMS	Turkey	1	60
P	19	Medical University of Gdansk	AMG	Poland	1	60
P	21	Fakultni nemocnice Brno	FNB	Czech Republic	1	60
P	22	Aarhus University Hospital	AUH	Denmark	1	60
P	23	University of Newcastle upon Tyne	UNEW	UK	1	60
P	24	National University of Ireland, Galway	NUI	Ireland	1	60
P	25	Université Victor Segalen Bordeaux 2	UVSB	France	1	60
P	26	Helsinki University Central Hospital	HUCH	Finland	1	60
P	27	Universitá degli Studi di Torino	UNITO	Italy	1	60
P	28	Jagiellonian University, Medical College	JUMC	Poland	1	60
P	29	Hospital Universitario de la Princesa	HUP	Spain	1	60

P	30	Klinikum Kreuzschwestern Wels GmbH	KKGW	Austria	1	60
P	31	University of Bern	UBERN	Switzerland	1	60

AML (WP 5)

LP	32	Universitätsklinikum Münster	UKM	Germany	1	60
LP	33	University of Wales, College of Medicine	UWCM	UK	1	60
LP	34	Fundación Hospital Universitario “La Fe”	LAFE	Spain	1	60
P	35	Universitá degli Studi di Roma Tor Vergata	UTV	Italy	1	60
P	36	Karolinska Institutet	KI	Sweden	1	60
P	10	Katholieke Universiteit Leuven	KUL	Belgium	1	60
P	37	Stichting Katholieke Universiteit, University Medical Center Nijmegen	UMCN	Netherlands	1	60
P	38	Universität Ulm	UULM	Germany	1	60
P	39	Technische Universität Dresden	TUD	Germany	1	60
P	40	Hopital Avicenne (CHU Paris 13)	HOA	France	1	60
P	41	Medizinische Hochschule Hannover	MHH	Germany	1	60
P	22	Aarhus University Hospital	AUH	Denmark	1	60
P	43	Medical University of Silesia, Kattowice	SLAM	Poland	1	60
P	44	Université de Lausanne	UNIL	Switzerland	1	60
P	45	Medizinische Universität Wien	MUW	Austria	1	60
P	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60
P	14	Erasmus University Medical Center Rotterdam	EMCR	Netherlands	1	60
P	46	Dipartimento di Biotecnologie Cellulari ed Ematologia, Università degli Studi di Roma "La Sapienza"	DBCLS	Italy	1	60
P	47	Universität Leipzig	ULZ	Germany	1	60
P	48	VU Academic Medical Center	VUMC	Netherlands	1	60
P	49	Fund for Medical Research Development of Infrastructure and Health Services, Rambam Medical Center	FMRR	Israel	1	60
P	50	National Research Center for Hematology	NRSH	Russia	1	60
P	51	Institut de Recerca de l´Hospital de la Santa Creu i Sant Pau	IRSC	Spain	1	60
P	52	Leiden University Medical Center	LUMC	Netherlands	1	60
P	53	Université Pierre et Marie Curie 6	UPMC	France	1	60

ALL (WP 6)

LP	2	Universitätsklinikum Frankfurt	UKF	Germany	1	60
LP	54	Azienda Ospedaliera-Ospedali Riuniti di Bergamo	OORB	Italy	1	60
LP	44	Université de Lausanne	UNIL	Switzerland	1	60
LP	46	Dipartimento di Biotecnologie Cellulari ed Ematologia, Università degli Studi di Roma "La Sapienza"	DBCLS	Italy	1	60
LP	52	Leiden University Medical Center	LUMC	Netherlands	1	60
P	55	University Medical Center Utrecht	UMCU	Netherlands	1	60
P	56	Association Publique-Hôpitaux de Paris	APHP	France	1	60
P	58	Centre Hospitalier Universitaire d´Angers	CHUA	France	1	60
P	59	University Hospital Center, Rebro, Zagreb	UHCR	Croatia	1	60
P	7	Uppsala Universitet	UU	Sweden	1	60

P	60	The Maria Sklodowska-Curie Memorial Cancer Center Institute of Oncol.	MSCM	Poland	1	60
P	70	Insitut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol	ICOH	Spain	1	60

CLL (WP 7)

LP	61	Institut Pasteur	IP	France	1	60
LP	38	Universität Ulm	UULM	Germany	1	60
LP	62	Universität Köln	KUK	Germany	1	60
P	63	HS Rigshospitalet	HSR	Denmark	1	60
P	64	Universitá Vita-Salute San Raffaele	UVSR	Italy	1	60
P	65	Institute of Cancer Research	ICR	UK	1	60
P	40	Hopital Avicenne (CHU Paris 13)	HOA	France	1	60
P	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	45	Medizinische Universität Wien	MUW	Austria	1	60
P	36	Karolinska Institutet	KI	Sweden	1	60
P	12	Hospital Clinic Provincial de Barcelona	HCPB	Spain	1	60
P	66	Royal Bournemouth and Christchurch Hospital NHS Trust	RBH	UK	1	60
P	67	Uniwersytet Medyczny w Lodzi	UMWL	Poland	1	60
P	68	Centre Hospitalier Universitaire de Caen	CHUC	France	1	60
P	46	Dipartimento di Biotecnologie Cellulari ed Ematologia, Università degli Studi di Roma "La Sapienza"	DBCLS	Italy	1	60
P	69	Academisch Ziekenhuis bij de Universiteit van Amsterdam	AZUA	Netherlands	1	60

MDS (WP 8)

LP	37	Stichting Katholieke Universiteit, Univ. Medical Center Nijmegen	UMCN	Netherlands	1	60
P	16	Imperial College London	ICSMT	UK	1	60
P	71	St. Johannes Hospital Duisburg	SJH	Germany	1	60
P	72	Fondazione Collegio Ghislieri	FCG	Italy	1	60
P	98	Universita degli Studi di Pavia	UNIPV	Italy	1	60
P	73	University of Dundee	UOD	UK	1	60
P	98	Universita degli Studi di Pavia	UNIPV	Italy	1	60
P	40	Hopital Avicenne (CHU Paris 13)	HOA	France	1	60
P	41	Medizinische Hochschule Hannover	MHH	Germany	1	60
P	74	Heinrich-Heine-Universität Düsseldorf, Universitätsklinikum	UKD	Germany	1	60
P	2	Universitätsklinikum Frankfurt	UKF	Germany	1	60
P	36	Karolinska Institutet	KI	Sweden	1	60
P	93	Lunds Universitet	ULUND	Sweden	1	60
P	83	Universitätsklinikum Freiburg	UHF	Germany	1	60
P	75	King´s College London	KCL	UK	1	60
P	48	VU Academic Medical Center	VUMC	Netherlands	1	60
P	76	Centre Hospitalier-Regional, Universitaire de Lille	CHUL	France	1	60
P	34	Fundación Hospital Universitario “La Fe”	LAFE	Spain	1	60
P	10	Katholieke Universiteit Leuven	KUL	Belgium	1	60

CMPD (WP 9)

LP	54	Azienda Ospedaliera-Ospedali Riuniti di Bergamo	OORB	Italy	1	60
LP	77	IRCCS Policlinico S. Matteo	IRCCS	Italy	1	60

P	7	Uppsala Universitet	UU	Sweden	1	60
P	40	Hopital Avicenne (CHU Paris 13)	HOA	France	1	60
P	12	Hospital Clínic i Provincial de Barcelona	HCPB	Spain	1	60
P	78	University of Southampton	SOTON	UK	1	60
P	79	Azienda Ospedaliera Ospedale San Martino	OSM	Italy	1	60
P	45	Medizinische Universität Wien	MUW	Austria	1	60
P	38	Universität Ulm	UULM	Germany	1	60
P	100	Odense University Hospital	OUH	Denmark	1	60
P	41	Medizinische Hochschule Hannover	MHH	Germany	1	60
P	81	Institut National de la Santé et de la Recherche Médicale	INSERM	France	1	60
P	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60
P	83	Universitätsklinikum Freiburg	UHF	Germany	1	60
P	84	University of Sheffield	UOSH	UK	1	60
P	62	Universität Köln	KUK	Germany	1	60

Diagnostic platform (WP 10)

LP	85	Université Henri Poincaré Nancy 1	UHP	France	1	60
LP	86	St. Marien-Krankenhaus Siegen gem. GmbH	SMKS	Germany	1	60
P	56	Association Publique-Hôpitaux de Paris	APHP	France	1	60
P	123	St. Antonius-Hospital Eschweiler	SAHE	Germany	1	60
P	45	Medizinische Universität Wien	MUW	Austria	1	60
P	88	Charité-Universitätsmedizin Berlin	CUB	Germany	1	60
P	65	Institute of Cancer Research	ICR	UK	1	60
P	87	Universidad de Salamanca	USAL	Spain	1	60
P	36	Karolinska Institutet	KI	Sweden	1	60
P	14	Erasmus University Medical Center Rotterdam	EMCR	Netherlands	1	60

Cytogenetics (WP 11)

LP	45	Medizinische Universität Wien	MUW	Austria	1	60
LP	89	Philipps-Universität Marburg	PUM	Germany	1	60
LP	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	63	HS Rigshospitalet	HSR	Denmark	1	60
P	51	Institut de Recerca de l´Hospital de la Santa Creu i Sant Pau	IRSC	Spain	1	60
P	14	Erasmus University Medical Center Rotterdam	EMCR	Netherlands	1	60
P	90	Centre Hospitalier Universitaire de Toulouse, Hotel-Dieu Saint Jaques	CHUT	France	1	60
P	75	King´s College London	KCL	UK	1	60
P	91	Children´s Cancer Research Institute	CCRI	Austria	1	60
P	10	Katholieke Universiteit Leuven	KUL	Belgium	1	60
P	92	Justus-Liebig-Universität, Giessen	JLU	Germany	1	60
P	9	Université de Poitiers	UNPO	France	1	60
P	93	Lunds Universitet	ULUND	Sweden	1	60
P	44	Université de Lausanne	UNIL	Switzerland	1	60
P	94	University of Helsinki	UHHI	Finland	1	60
P	95	Queen Mary University of London	QMUL	UK	1	60
P	96	Università degli Studi di Perugia	UDSP	Italy	1	60
P	97	Università degli Studi di Bari	UNIBA	Italy	1	60
P	81	Institut National de la Santé et de la Recherche Médicale	INSERM	France	1	60
P	41	Medizinische Hochschule Hannover	MHH	Germany	1	60

P	51	Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	IRSC	Spain	1	60
P	38	Universität Ulm	UULM	Germany	1	60

Minimal residual disease (WP 12)

LP	75	King´s College London	KCL	UK	1	60
P	7	Uppsala Universitet	UU	Sweden	1	60
P	98	Universita degli Studi di Pavia	UNIPV	Italy	1	60
P	78	University of Southampton	UOS	UK	1	60
P	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60
P	22	Aarhus University Hospital	AUH	Denmark	1	60
P	16	Imperial College London	ICSMT	UK	1	60
P	99	University Hospital Schleswig-Holstein, Campus Kiel	UKSH	Germany	1	60
P	35	Universitá degli Studi di Roma Tor Vergata	UTV	Italy	1	60
P	112	Jules Bordet Institute-Free University of Brussels	JBI	Belgium	1	60
P	8	Universitá di Bologna- Unita Complessa di Istituti di Cardiologia ed Ematologia	UCCE	Italy	1	60
P	51	Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	IRSC	Spain	1	60
P	48	VU Academic Medical Center	VUMC	Netherlands	1	60
P	100	Odense University Hospital	OUH	Denmark	1	60
P	101	CEINGE Biotecnologie avanzate s.c.a.r.l.	CEINGE	Italy	1	60
P	76	Centre Hospitalier-Régional, Universitaire de Lille	CHUL	France	1	60
P	28	Jagiellonian University, Medical College	JUMC	Poland	1	60
P	27	Università degli Studi di Torino	UNITO	Italy	1	60
P	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	39	Technische Universität Dresden	TUD	Germany	1	60
P	102	Central Manchester and Manchester Children´s University Hospitals NHS Trust	CMMC	UK	1	60
P	14	Erasmus University Medical Center Rotterdam	EMCR	Netherlands	1	60

Gene profiling (WP 13)

LP	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	103	European Molecular Biology Laboratory	EMBL	UK	1	60
P	7	Uppsala Universitet	UU	Sweden	1	60
P	104	Università degli Studi di Padova	UNIP	Italy	1	60
P	61	Institut Pasteur	IP	France	1	60
P	38	Universität Ulm	UULM	Germany	1	60
P	105	University of Modena and Reggio Emilia	UMRE	Italy	1	60
P	106	Fundación de Investigación del Cancer	FICUS	Spain	1	60
P	2	Universitätsklinikum Frankfurt	UKF	Germany	1	60
P	37	Stichting Katholieke Universiteit, Univ. Medical Center Nijmegen	UMCN	Netherlands	1	60
P	16	Imperial College London	ICSMT	UK	1	60
P	33	University of Wales, College of Medicine	UWCM	UK	1	60
P	89	Philipps-Universität Marburg	PUM	Germany	1	60
P	41	Medizinische Hochschule Hannover	MHH	Germany	1	60

P	46	Dipartimento di Biotecnologie Cellulari ed Ematologia, Università degli Studi di Roma "La Sapienza"	DBCLS	Italy	1	60
P	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60

Stem cell transplantation (WP 14)

LP	16	Imperial College London	ICSMT	UK	1	60
LP	17	University of Basel/University Hospitals	UNIBAS	Switzerland	1	60
LP	47	Universität Leipzig	ULZ	Germany	1	60
P	79	Genova Ospedale San Martino	GOSM	Italy	1	60
P	52	Leiden University Medical Center	LUMC	Netherlands	1	60
P	107	Göteborg University	GU	Sweden	1	60
P	37	Stichting Katholieke Universiteit, University Medical Centre Nijmegen	UMCN	Netherlands	1	60
P	36	Karolinska Institutet	KI	Sweden	1	60
P	108	Association pour la Recherche sur les Transplantations Medullaires	ARTM	France	1	60
P	45	Medizinische Universität Wien	MUW	Austria	1	60
P	46	Dipartimento di Biotecnologie Cellulari ed Ematologia, Università degli Studi di Roma "La Sapienza"	DBCLS	Italy	1	60
P	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60
P	43	Medical University of Silesia, Katowice	SLAM	Poland	1	60
P	109	Akademia Medyczna w Warszawie, Medical University of Warsaw	AMW	Poland	1	60
P	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	59	University Hospital Center, Rebro, Zagreb	UHCR	Kroatia	1	60
P	110	St. Laszlo Hospital	SLH	Hungary	1	60
P	21	Fakultni nemocnice Brno	FNB	Czech Republic	1	60
P	49	Fund for Medical Research Development of Infrastructure and Health Services, Rambam Medical Center	FMRR	Israel	1	60
P	26	Helsinki University Central Hospital	HUCH	Finland	1	60
P	51	Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	IRSC	Spain	1	60
P	7	Uppsala Universitet	UU	Sweden	1	60
P	12	Hospital Clínic i Provincial de Barcelona	HCPB	Spain	1	60

Supportive care/anti-infection prophylaxis and treatment (WP 15)

LP	36	Karolinska Institutet	KI	Sweden	1	60
LP	111	Eberhard-Karls Universität Tübingen	EKUT	Germany	1	60
P	18	Ankara University	AUMS	Turkey	1	60
P	2	Universitätsklinikum Frankfurt	UKF	Germany	1	60
P	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60
P	56	Association Publique-Hôpitaux de Paris	APHP	France	1	60
P	55	University Medical Center Utrecht	UMCU	Netherlands	1	60
P	17	University of Basel/University Hospitals	UNIBAS	Switzerland	1	60
P	115	Azienda Ospedaliera San Camillo-Forlanini	OSCF	Italy	1	60
P	10	Katholieke Universiteit Leuven	KUL	Belgium	1	60
P	51	Institut de Recerca de l´Hospital de la Santa Creu i sant Pau	IRSC	Spain	1	60
P	88	Charité-Universitätsmedizin Berlin	CUB	Germany	1	60

P	15	Johannes Gutenberg-Universität Mainz	JOGU	Germany	1	60
P	116	University of Genova	UOG	Italy	1	60
P	117	University College London	UCL	UK	1	60

Treatment Research/New Targets/New Drugs (WP 16)

LP	32	Universitätsklinikum Münster	UKM	Germany	1	60
P	16	Imperial College London	ICSMT	UK	1	60
P	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	111	Eberhard-Karls Universität Tübingen	EKUT	Germany	1	60
P	78	University of Southampton	SOTON	UK	1	60
P	56	Association Publique-Hôpitaux de Paris	APHP	France	1	60
P	88	Charité-Universitätsmedizin Berlin	CUB	Germany	1	60
P	118	Technische Universität München	TUM	Germany	1	60
P	119	Universitätsklinikum Hamburg-Eppendorf	UKE	Germany	1	60
P	2	Universitätsklinikum Frankfurt	UKF	Germany	1	60
P	62	Universität Köln	KUK	Germany	1	60
P	100	Odense University Hospital	OUH	Denmark	1	60
P	114	Hebrew University of Jerusalem	HUJI	Israel	1	60
P	120	Peptor LTD	PEPT	Israel	1	60
P	37	Stichting Katholieke Universiteit, Univ. Medical Center Nijmegen	UMCN	Netherlands	1	60
P	38	Universität Ulm	UULM	Germany	1	60
P	39	Technische Universität Dresden	TUD	Germany	1	60
P	65	Institute of Cancer Research	ICR	UK	1	60
P	122	Innsbruck Medical University	IMU	Austria	1	60

Registries, Epidemiology, Metaanalysis, Prognosis (WP 17)

LP	5	Ludwig-Maximilians-Universität München	LMU	Germany	1	60
P	8	Universitá di Bologna- Unita Complessa di Istituti di Cardiologia ed Ematologia	UCCE	Italy	1	60
P	9	Université de Poitiers	UNPO	France	1	60

Guidelines Platform (WP 18)

LP	23	University of Newcastle upon Tyne	UNEW	UK	1	60
LP	108	Association pour la Recherche sur les Transplantations Medullaires	ARTM	France	1	60
P	71	St. Johannes Hospital Duisburg	SJH	Germany	1	60
P	54	Azienda Ospedaliera-Ospedali Riuniti di Bergamo	OORB	Italy	1	60
P	32	Universitätsklinikum Münster	UKM	Germany	1	60
P	37	Stichting Katholieke Universiteit, Univ. Medical Center Nijmegen	UMCN	Netherlands	1	60
P	61	Institut Pasteur	IP	France	1	60
P	38	Universität Ulm	UULM	Germany	1	60
P	45	Medizinische Universität Wien	MUW	Austria	1	60
P	75	King´s College London	KCL	UK	1	60
P	1	Ruprecht-Karls-Universität Heidelberg	UHEI	Germany	1	60
P	2	Universitätsklinikum Frankfurt	UKF	Germany	1	60
P	66	Royal Bournemouth and Christchurch Hospital NHS Trust	RBH	UK	1	60

3.2 List of associated scientists

Scientist Role	Participant number (n=117)	Scientist Name	Scientist short name	Country	Date enter project	Date exit project
NMC (WP 1)						
LP	1	R. Hehlmann	HEH	Germany	1	60
LP	1	U. Berger*	BER	Germany	1	60
P	1	A. Hochhaus	HOC	Germany	1	60
P	1	A. Reiter	REIT	Germany	1	60
P	1	S. Weinreich	WEI	Germany	1	60
ELIC (WP 2)						
LP	2	N. Gökbuget*	GOE	Germany	1	60
P	2	A. Böhme*	BOE	Germany	1	60
P	2	A. Hellenbrecht*	HEL	Germany	1	60
P	4	U. Holtkamp*	HOL	Germany	1	60
P	2	H. Martin	MARH	Germany	1	60
P	2	U. Scheuring	SCG	Germany	1	60
P	3	G. Zini*	ZIN	Italy	1	60
CICS (WP 3)						
LP	5	T. Müller	MUE	Germany	1	60
LP	5	K. Überla	UEB	Germany	1	60
LP	5	M. Dugas	DUG	Germany	1	60
P	6	G. Gell	GEL	Austria	1	60
P	5	J. Hasford	HAS	Germany	1	60
P	121	M. Ackermann	ACK	Germany	1	60
CML (WP4)						
LP	7	B. Simonsson	SIM	Sweden	1	60
LP	8	M. Baccarani	BAC	Italy	1	60
LP	9	F. Guilhot	GUI	France	1	60
LP	1	A. Hochhaus	HOC	Germany	1	60
LP	1	R. Hehlmann	HEH	Germany	1	60
P	10	M. Boogaerts	BOO	Belgium	1	60
P	79	A. Carella	CAR	Italy	1	60
P	12	F. Cervantes	CER	Spain	1	60
P	13	A. Colita	COL	Romania	1	60
P	14	J.J. Cornelissen	CORN	Netherlands	1	60
P	15	T. Fischer	FIS	Germany	1	60
P	16	J.M. Goldman	GOL	UK	1	60
P	17	A. Gratwohl	GRA	Switzerland	1	60
P	5	J. Hasford	HAS	Germany	1	60
P	18	I.C. Haznedaroglu	HAZ	Turkey	1	60
P	19	A. Hellmann	HELL	Poland	1	60
P	21	J. Mayer	MAY	Czech Republic	1	60
P	22	J.L. Nielsen	NIE	Denmark	1	60
P	23	S.G. O'Brien	OBR	UK	1	60
P	24	M.E. O'Dwyer	ODW	Ireland	1	60
P	25	F. X. Mahon	MAHO	France	1	60
P	26	T. Ruutu	RUU	Finland	1	60
P	27	G. Saglio	SAG	Italy	1	60

P	28	B. Skotnicki	SKO	Poland	1	60
P	29	J.-L. Steegmann	STE	Spain	1	60
P	30	J. Thaler	THA	Austria	1	60
P	31	A. Tobler	TOBA	Switzerland	1	60
P	10	G. Verhoef	VER	Belgium	1	60

AML (WP 5)

LP	32	T. Büchner	BUE	Germany	1	60
LP	33	A. Burnett	BUR	UK	1	60
LP	34	M. Sanz	SAN	Spain	1	60
P	35	S. Amadori	AMA	Italy	1	60
P	36	M. Björkholm	BJO	Sweden	1	60
P	10	M. Boogaerts	BOO	Belgium	1	60
P	37	T. de Witte	DEW	Netherlands	1	60
P	38	H. Döhner	DOE	Germany	1	60
P	39	G. Ehninger	EHN	Germany	1	60
P	40	P. Fenaux	FEN	France	1	60
P	41	A. Ganser	GAN	Germany	1	60
P	22	P. Hokland	HOK	Denmark	1	60
P	43	J. Holowiecki	HOLO	Poland	1	60
P	44	T. Kovacsovics	KOV	Switzerland	1	60
P	45	K. Lechner	LEC	Austria	1	60
P	1	E. Lengfelder*	LEN	Germany	1	60
P	14	B. Löwenberg	LOE	Netherlands	1	60
P	46	F. Mandelli	MAN	Italy	1	60
P	47	D. Niederwieser	NIED	Germany	1	60
P	48	G.J. Ossenkoppele	OSS	Netherlands	1	60
P	49	J.M. Rowe	ROW	Israel	1	60
P	50	V. Savchenko	SAV	Russia	1	60
P	51	J. Sierra	SIE	Spain	1	60
P	45	P. Valent	VAL	Austria	1	60
P	52	R. Willemze	WILL	Netherlands	1	60
P	53	J.P. Marie	JPM	France	1	60

ALL (WP 6)

LP	2	N. Gökbuget*	GOE	Germany	1	60
LP	54	R. Bassan	BAS	Italy	1	60
LP	2	D. Hoelzer	HOE	Germany	1	60
LP	44	T. Kovacsovics	KOV	Switzerland	1	60
LP	46	F. Mandelli	MAN	Italy	1	60
LP	70	J.M. Ribera	RIB	Spain	1	60
LP	52	R. Willemze	WILL	Netherlands	1	60
P	46	L. Annino*	ANN	Italy	1	60
P	55	A. Dekker	DEK	Netherlands	1	60
P	56	H. Dombret	DOM	France	1	60
P	46	R. Foa	FOA	Italy	1	60
P	58	N. Ifrah	IFR	France	1	60
P	59	B. Labar	LAB	Croatia	1	60
P	46	G. Meloni*	MEL	Italy	1	60
P	7	B. Smedmyr	SME	Sweden	1	60
P	60	J. Walewski	WAL	Poland	1	60

CLL (WP 7)

LP	61	G. Dighiero	DIG	France	1	60
LP	38	H. Döhner	DOE	Germany	1	60
LP	62	M. Hallek	HAL	Germany	1	60

P	63	A. Buhl*	BUH	Denmark	1	60
P	64	F. Caligaris-Cappio	CAL	Italy	1	60
P	65	D. Catovsky	CAT	UK	1	60
P	40	F. Cymbalista*	CYB	France	1	60
P	5	B. Emmerich	EMM	Germany	1	60
P	46	R. Foa	FOA	Italy	1	60
P	45	A. Gaiger	GAI	Austria	1	60
P	63	C. Geisler	GEI	Denmark	1	60
P	45	U. Jaeger	JAE	Austria	1	60
P	63	J. Jurlander	JUR	Denmark	1	60
P	36	E. Kimby	KIM	Sweden	1	60
P	65	E. Matutes*	MAT	UK	1	60
P	12	E. Montserrat	MON	Spain	1	60
P	36	A. Österborg	OST	Sweden	1	60
P	66	D. Oscier	OSC	UK	1	60
P	67	T. Robak	ROB	Poland	1	60
P	38	S. Stilgenbauer	STI	Germany	1	60
P	68	X. Troussard	TRO	France	1	60
P	69	M.H. Van Oers	VANO	Netherlands	1	60

MDS (WP 8)

LP	37	T. de Witte	DEW	Netherlands	1	60
P	16	J. Apperley*	APP	UK	1	60
P	71	C. Aul	AUL	Germany	1	60
P	72	C. Bernasconi	BERN	Italy	1	60
P	98	P. Bernasconi	BERP	Italy	1	60
P	73	D. Bowen	BOW	UK	1	60
P	98	M. Cazzola	CAZ	Italy	1	60
P	40	P. Fenaux	FEN	France	1	60
P	41	A. Ganser	GAN	Germany	1	60
P	74	N. Gattermann	GAT	Germany	1	60
P	74	U. Germing	GERM	Germany	1	60
P	88	W.-K. Hofmann	HOF	Germany	1	60
P	36	E. Hellström-Lindberg*	HELI	Sweden	1	60
P	93	S. E. Jacobsen	JACO	Sweden	1	60
P	37	J.H. Jansen	JAN	Netherlands	1	60
P	83	M. Lübbert	LUEB	Germany	1	60
P	75	G. Mufti	MUFT	UK	1	60
P	48	G.J. Ossenkoppele	OSS	Netherlands	1	60
P	75	R.A. Padua*	PAD	UK	1	60
P	76	C. Preudhomme	PRE	France	1	60
P	34	G. Sanz	SANZ	Spain	1	60
P	10	G. Verhoef	VER	Belgium	1	60

CMPD (WP 9)

LP	54	T. Barbui	BAR	Italy	1	60
LP	77	G. Barosi	BARO	Italy	1	60
LP	54	G. Finazzi	FIN	Italy	1	60
P	7	G. Birgegard	BIRG	Sweden	1	60
P	40	J. Briere	BRIE	France	1	60
P	12	F. Cervantes	CER	Spain	1	60
P	78	N.C.P. Cross	CRO	UK	1	60
P	79	F. Frassoni	FRA	Italy	1	60
P	45	H. Gisslinger	GIS	Austria	1	60
P	38	M. Griesshammer	GRIE	Germany	1	60
P	100	H. Hasselbalch	HASS	Denmark	1	60
P	41	H.H. Kreipe	KRE	Germany	1	60

P	81	M.C. Le Bousse-Kerdilès*	LEB	France	1	60
P	1	E. Lengfelder*	LEN	Germany	1	60
P	83	H. Pahl*	PAH	Germany	1	60
P	54	A. Rambaldi	RAMB	Italy	1	60
P	84	T. Reilly	REIL	UK	1	60
P	1	A. Reiter	REIT	Germany	1	60
P	83	A. Schmitt-Gräff*	SCHG	Germany	1	60
P	62	J. Thiele	THIEL	Germany	1	60

Diagnostic platform (WP 10)

LP	85	M.C. Béné*	BEN	France	1	60
LP	86	W. Gassmann	GAS	Germany	1	60
P	56	M.-T. Daniel*	DAN	France	1	60
P	123	R. Fuchs	FUC	Germany	1	60
P	45	W. Knapp	KNA	Austria	1	60
P	88	W.-D. Ludwig	LUD	Germany	1	60
P	65	E. Matutes*	MAT	UK	1	60
P	87	A. Orfao	ORF	Spain	1	60
P	36	A. Porwit-MacDonald*	POR	Sweden	1	60
P	14	M. van`t Veer*	VANV	Netherlands	1	60

Cytogenetics (WP 11)

LP	45	C. Fonatsch*	FON	Austria	1	60
LP	89	H. Rieder	RIE	Germany	1	60
LP	5	C. Schoch*	SCHO	Germany	1	60
P	63	M. Andersen*	AND	Denmark	1	60
P	51	A. Aventin*	AVE	Spain	1	60
P	14	H.B. Beverloo*	BEV	Netherlands	1	60
P	90	N. Dastugue*	DAS	France	1	60
P	75	D. Grimwade	GRI	UK	1	60
P	91	O. Haas	HAA	Austria	1	60
P	10	A. Hagemeijer*	HAG	Belgium	1	60
P	92	J. Harbott	HARB	Germany	1	60
P	9	J.-L. Huret	HUR	France	1	60
P	93	B. Johansson	JOH	Sweden	1	60
P	44	M. Jotterand*	JOT	Switzerland	1	60
P	94	S. Knuutilla	KNU	Finland	1	60
P	95	D.M. Lillington*	LIL	UK	1	60
P	96	C. Mecucci*	MEC	Italy	1	60
P	93	F. Mitelman	MIT	Sweden	1	60
P	63	J. Pedersen-Bjergaard	PED	Denmark	1	60
P	97	M. Rocchi	ROC	Italy	1	60
P	81	P. Romana	ROM	France	1	60
P	41	B. Schlegelberger*	SCHL	Germany	1	60
P	38	S. Stilgenbauer	STI	Germany	1	60

Minimal residual disease (WP 12)

LP	75	D. Grimwade	GRI	UK	1	60
P	7	G. Barbany*	BARB	Sweden	1	60
P	98	P. Bernasconi	BERA	Italy	1	60
P	78	N.C.P. Cross	CRO	UK	1	60
P	1	A. Hochhaus	HOC	Germany	1	60
P	22	P. Hokland	HOK	Denmark	1	60
P	16	J. Kaeda	KAE	UK	1	60
P	99	M. Kneba	KNE	Germany	1	60
P	35	F. Lo Coco	LOC	Italy	1	60

P	112	P. Martiat	MART	Belgium	1	60
P	8	G. Martinelli	MARG	Italy	1	60
P	75	G.J. Mufti	MUFT	UK	1	60
P	51	J. Nomdedeu	NOM	Spain	1	60
P	48	G.J. Ossenkoppele	OSS	Netherlands	1	60
P	75	R.A. Padua*	PAD	UK	1	60
P	100	N. Pallisgaard	PAL	Denmark	1	60
P	101	F. Pane	PAN	Italy	1	60
P	76	C. Preudhomme	PRE	France	1	60
P	1	A. Reiter	REIT	Germany	1	60
P	28	T. Sacha	SACH	Poland	1	60
P	27	G. Saglio	SAG	Italy	1	60
P	5	S. Schnittger*	SCHN	Germany	1	60
P	39	C. Thiede	THIE	Germany	1	60
P	102	K. Tobal	TOB	UK	1	60
P	14	V. van der Velden	VEL	Netherlands	1	60
P	14	J.J.M. van Dongen	DON	Netherlands	1	60
P	102	J. Yin	YIN	UK	1	60

Gene profiling (WP 13)

LP	5	T. Haferlach	HAF	Germany	1	60
LP	5	W. Hiddemann	HID	Germany	1	60
P	103	R. Apweiler	APW	UK	1	60
P	7	G. Barbany*	BARB	Sweden	1	60
P	104	G. Basso	BASS	Italy	1	60
P	61	G. Dighiero	DIG	France	1	60
P	38	H. Döhner	DOE	Germany	1	60
P	5	M. Dugas	DUG	Germany	1	60
P	105	S. Ferrari	FER	Italy	1	60
P	46	R. Foa	FOA	Italy	1	60
P	106	J.M. Hernandez Rivas	HER	Spain	1	60
P	88	W.-K. Hofmann	HOF	Germany	1	60
P	37	J.H. Jansen	JAN	Netherlands	1	60
P	16	J.V. Melo*	MELO	UK	1	60
P	33	K. Mills	MIL	UK	1	60
P	89	A. Neubauer	NEU	Germany	1	60
P	41	B. Schlegelberger*	SCHL	Germany	1	60
P	1	W. Seifarth	SEI	Germany	1	60

Stem cell transplantation (WP 14)

LP	16	J. Apperley*	APP	UK	1	60
LP	17	A. Gratwohl	GRA	Switzerland	1	60
LP	47	D. Niederwieser	NIED	Germany	1	60
P	79	A. Bacigalupo	BACI	Italy	1	60
P	52	R. Brand	BRA	Netherlands	1	60
P	107	M. Brune	BRU	Sweden	1	60
P	37	T. de Witte	DEW	Netherlands	1	60
P	79	F. Frassoni	FRA	Italy	1	60
P	36	G. Gahrton	GAH	Sweden	1	60
P	108	E. Gluckman*	GLU	France	1	60
P	45	H. Greinix*	GREI	Austria	1	60
P	46	C. Guglielmi	GUG	Italy	1	60
P	1	A.D. Ho	AHO	Germany	1	60
P	43	J. Holowiecki	HOLO	Poland	1	60
P	109	W. Jedrzejckaz	JED	Poland	1	60
P	5	H.J. Kolb	KOL	Germany	1	60
P	59	B. Labar	LAB	Croatia	1	60

P	12	F. MacDonald*	MCD	Spain	1	60
P	110	T. Masszi	MAS	Hungary	1	60
P	21	J. Mayer	MAY	Czech Republic	1	60
P	49	J. M. Rowe	ROW	Israel	1	60
P	26	T. Ruutu	RUU	Finland	1	60
P	51	J. Sierra	SIE	Spain	1	60
P	7	B. Simonsson	SIM	Sweden	1	60
P	12	A. Urbano-Ispizua	URB	Spain	1	60

Supportive care/anti-infection prophylaxis and treatment (WP 15)

LP	36	P. Ljungman	LJU	Sweden	1	60
LP	111	H. Einsele	EIN	Germany	1	60
P	112	H. Akan	AKA	Turkey	1	60
P	2	A. Böhme*	BOE	Germany	1	60
P	1	D. Buchheidt	BUC	Germany	1	60
P	56	C. Cordonnier*	COR	France	1	60
P	55	A. Dekker	DEK	Netherlands	1	60
P	17	A. Gratwohl	GRA	Switzerland	1	60
P	115	A. Locasciulli*	LOC	Italy	1	60
P	10	J. Maertens	MAE	Belgium	1	60
P	51	R. Martino	MARR	Spain	1	60
P	88	G. Maschmeyer	MASC	Germany	1	60
P	17	P. Reusser	REU	Switzerland	1	60
P	15	A. Ullmann	ULL	Germany	1	60
P	116	C. Viscoli	VIS	Italy	1	60
P	117	K. Ward*	WAR	UK	1	60

Treatment Research/New Targets/New Drugs (WP 16)

LP	32	W. Berdel	BERD	Germany	1	60
LP	32	H. Serve	SER	Germany	1	60
P	16	J. Apperley*	APP	UK	1	60
P	5	G. Behre	BEH	Germany	1	60
P	111	T. Brümmendorf	BRUM	Germany	1	60
P	78	N.C. P. Cross	CRO	UK	1	60
P	56	L. Degos	DEG	France	1	60
P	88	B. Dörken (A. Pezzuto)	DOR	Germany	1	60
P	118	J. Duyster	DUY	Germany	1	60
P	119	W. Fiedler	FIE	Germany	1	60
P	2	N. Gökbuget*	GOE	Germany	1	60
P	1	U. Berger*	BER	Germany	1	60
P	62	M. Hallek	HAL	Germany	1	60
P	100	H. Hasselbalch	HASS	Denmark	1	60
P	114	A. Levitzki	LEV	Israel	1	60
P	120	N. Livnah	LIV	Israel	1	60
P	37	P. Muus*	MUU	Netherlands	1	60
P	2	O.G. Ottmann	OTT	Germany	1	60
P	114	R. Reuven	REUV	Israel	1	60
P	38	R. Schlenk	SCHK	Germany	1	60
P	39	C. Thiede	THIE	Germany	1	60
P	65	A. Zelent	ZEL	UK	1	60
P	122	H. Zwierzina	ZWI	Austria	1	60

Registries, Epidemiology, Metaanalysis, Prognosis (WP 17)

LP	5	J. Hasford	HAS	Germany	1	60
P	8	F. Bonifazi*	BFZ	Italy	1	60
P	5	M. Dugas	DUG	Germany	1	60

P	9	J. Guilhot*	GUIJ	France	1	60
P	5	D. Hölzel	HOELZ	Germany	1	60
P	5	D. Messerer*	MES	Germany	1	60
P	5	T. Müller	MUE	Germany	1	60
P	32	T. Büchner	BUE	Germany	1	60
P	33	A. Burnett	BUR	UK	1	60
P	34	M. Sanz	SAN	Spain	1	60

Guidelines Platform (WP 18)

LP	23	S.G. O´Brien	OBR	UK	1	60
LP	108	E. Gluckman*	GLU	France	1	60
P	71	C. Aul	AUL	Germany	1	60
P	54	T. Barbui	BAR	Italy	1	60
P	32	T. Büchner	BUE	Germany	1	60
P	37	T. de Witte	DEW	Netherlands	1	60
P	61	G. Dighiero	DIG	France	1	60
P	38	H. Döhner	DOE	Germany	1	60
P	45	C. Fonatsch*	FON	Austria	1	60
P	75	D. Grimwade	GRI	UK	1	60
P	1	R. Hehlmann	HEH	Germany	1	60
P	2	D. Hoelzer	HOE	Germany	1	60
P	66	D. Oscier	OSC	UK	1	60
P	1	U. Berger*	BER	Germany	1	60
P	1	A. Hochhaus	HOC	Germany	1	60
P	2	N. Gökbuget*	GOE	Germany	1	60

4. RELEVANCE OF THE OBJECTIVES OF THE SPECIFIC PROGRAMME AND / OR THEMATIC

LSH-2002-2.2.0-3: Networking for treatment and/or prevention clinical trials (phase I and II) aimed at improving clinical practice in the light of new molecular knowledge – NETWORK OF EXCELLENCE. *The main objective of the network will be to integrate acquired cross-disciplinary input, with the aim to facilitate its translation into improvements in the clinical context. Trials should be aimed at proof-of-principle.*

Emergence of molecular targeted therapy in leukemias

The treatment of leukemias has emerged as one of the most successful areas in oncology. Leukemias are the only cancers, in which molecular targeted therapy has been effective and revealed its "proof of principle". Thus, leukemias are regarded useful models for design of novel drug treatments with relevance to all forms of cancer. It is envisioned that a major expansion of leukemia research will provide a paradigm for solid tumors and such an investment will far exceed the frequency of leukemias.

In the last decade, great progress was made in understanding of signal transduction of deregulated growth factor receptors and the molecular events regulating hematopoietic differentiation. These new insights into pathophysiology of leukemias has led to the discovery of a multitude of potential targets awaiting to be tested in the clinic. All-trans retinoic acid exemplifies the first successful molecular therapeutic agent, which induces terminal differentiation of the leukemic blasts in acute promyelocytic leukemia (APL) and a complete remission by targeting of the retinoid acid receptor molecule, which is involved in the PML/RARA fusion gene.

Imatinib and beyond, an array of new targets

More recently, effective targeted therapy has been demonstrated by the introduction of imatinib as highly active therapeutic in chronic myelogenous leukemia (CML) and BCR-ABL+ acute lymphoblastic leukemia (ALL). Imatinib, which selectively inhibits a number of tyrosine kinases, induces unprecedented high hematological and cytogenetic response rates and its toxicity profile appears more attractive than of conventional drugs. Beyond ATRA therapy in APL and imatinib in CML and ALL the differentiation-inducing agents like inhibitors of histone deacetylases or arsenic trioxide appear promising approaches for the treatment of acute leukemias and will be investigated further. Besides having now compounds at hands capable of targeting the potentially causative defects in leukemia, monoclonal antibodies have recently been added to the armamentarium and show promise in the therapy of chronic lymphatic leukemia (CLL). Within the scope of this proposal, a number of other specific tyrosine kinase inhibitors, e.g., FLT3 inhibitors for the treatment of AML, Jak2 inhibitors for the treatment of ALL, Akt/PkB inhibitors for the treatment of several subgroups of leukemia and other molecules targeting the signal transduction pathways downstream of receptor tyrosine kinases will be evaluated.

Building an interdisciplinary network

Advances in understanding pathobiology of leukemias or antileukemic efficacy of potential new drugs have in many instances in the past relied on cross disciplinary exchange of clinical observations and cellular genetic or molecular findings. For instance, recurrent chromosomal translocations led to the definition of prognostic cytogenetic groups and the identification of fusion genes and –proteins underscoring the central role of the genes for the survival and differentiation of hematopoietic progenitor cells.

Thus, further investment in the characterization of molecular lesions identified by gene expression profiling or other sophisticated molecular techniques will identify new genetic defects and targets and will pave the way to novel therapeutic strategies. A multidisciplinary team approach involving scientists in various fields of leukemia research, i.e. drug discovery, leukemia diagnostics, molecular genetics, clinical trials methodology, and biostatistics, is urgently needed. It is critical to establish a network of expert laboratories at the European level that have long-standing experience, reputation and a close working relationship with clinical trials groups. Identification of leukemia-specific highly expressed molecular markers could yield important benefits in terms of patient care, by significantly extending the numbers of patients that could be subject to innovative treatment strategies, accelerating transfer of advances into the clinics. This could substantially change the face of leukemia trials, whereby risk-stratified treatment schedules determined by pre-treatment characteristics and validated prognostic markers could be further fine-tuned to the needs of the individual patient.

Optimization and integration of molecular therapeutics and conventional therapies
Even after the identification of a validated target, it takes 5-10 years to bring a new drug to trial. Thus, speeding up of this process is a major task of integrating activities. The assessment of antileukemic effects at a molecular level will also contribute to validate and compare different treatment regimens. Future progress in discoveries of relevant biomarkers and successful identification of candidate drugs on the basis of molecular lesions, however, requires an investment into setting up registries, diagnosis, prognosis, disease monitoring, and clinical trials platforms.

Clinical Trials Platform
The "Clinical Trials Platform" will integrate European expertise, explore and validate new therapeutic interventions with minimal side effects, and transfer research results to rapid applications in public health. With the current proposal a unique opportunity exists that essentially all leading leukemia trials groups for AML, ALL, CML, CLL, MDS, CMPD in Europe participate in the European Leukemia Network.

The major goals of the Clinical Trials Platform is to align these various national study groups by enhancing communication, facilitating exchange of knowledge such as protocols, current and future trials activities, improved access to clinical trials and streamlining trials methodology and statistical analysis in Europe, and lastly exploring new treatment strategies in leukemias. This is the first of multi-national platforms to be created for phase I and II drug development trials.

Overcoming fragmentation, standardizing diagnostics and therapies
Currently, fragmentation of therapeutic trials in Europe severely hampers any palpable progress, leads to duplications and redundancies, which make the whole process highly inefficient. Besides lacking common research strategies the major leukemia study groups nowadays sparsely interact by neglect of common minimum data sets in clinical trials, alignments of study designs and protocols. Stem cell transplantation is another case, where standardized conditioning protocols and transplant-related procedures could potentially yield significantly improved comparability of treatments. Furthermore, methodology in leukemia diagnostics, i.e. cytogenetics, morphology, immunophenotyping, and molecular genetics, lacks standardization and stringent evaluation by quality control rounds. Different treatment strategies in a given field of leukemia are not comparable in terms of minimal common data sets, which hampers data sharing for future metaanalyses and validation of prognostic factors.

Standardization of commonly employed diagnostic procedures and stringently applied standardized approaches to leukemia therapy is critically important and the most readily visible first step towards integration in Europe. Of course, a prerequisite to this endeavor is that beyond reaching a critical mass virtually all leukemia study groups are apt for full implementation. The European Leukemia Network provides a unique opportunity to establish standards in the different branches of leukemia research including stem cell transplantation, patient management and supportive care measures. This investment is highly cost effective, reshapes the whole European infrastructure and achieves long lasting sustainability and added value.

Public Health
One main objective of the network will be to integrate national and cross-disciplinary input and to facilitate its translation into improvements in the clinical context. The set-up of an European information and communication network will make a major contribution to public health and spread of excellence since the participating groups represent the major opinion leaders in their respective countries. By the promotion of information on new treatment approaches as evaluated in clinical trials earlier transfer of new knowledge in clinical practice will be achieved. Regional differences will be reduced by internet based information offers. Related issues such as such as leukemia in older patients, psycho-social aspects, palliative care can be addressed in cooperative projects. In addition information for leukemia patients and guidance of national support groups in European countries will be provided.

The European Added Value
In the current proposal all major leukemia trial networks and regional groups of the following European countries have committed themselves by written documentation to form a longstanding partnership in the European Leukemia Network with the aim of making a durable impact on reshaping clinical practice and existing research of leukemias in Europe on a world scale:

Austria, Belgium, Croatia, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Netherlands, Poland, Russia, Spain, Sweden, Switzerland, Turkey, United Kingdom and Israel.

Participating SMEs:
Peptor, Inc, Israel
Megapharm GmbH, Germany

Several indicators exist that the European Leukemia Network will have long lasting sustained impact on clinical and public health in Europe:

- **Critical mass:** The European Leukemia Network provides the infrastructure and the critical mass to overcome the widespread existing shortfalls currently faced with leukemia research in Europe.

- **Standardization:** will have direct implications on the therapeutic progress by successful, large clinical trials, metaanalyses of specific subaspects, the elaboration of prognostic scores, uniform data sets for study protocols, introduction of standards in molecular diagnostics, harmonization of transplant procedures, or the development of evidence based guidelines. While state-of- the-art leukemia therapy is becoming more and more complex networking will offer synergism and efficient problem-solving capacities. Lastly, advances in understanding gained would be directly applicable to many other tumors.

- **Registries:** rational drug development requires a detailed understanding of subsets with regard to disparities in prognosis, treatment response and outcome. It is therefore perceived that the establishment of European registries containing large comprehensive sets of clinical and lab data collected in a uniform standardized fashion will specifically address the growing needs to better risk stratify patients in the genomic era, to optimize conventional as well as emerging therapies and to overcome barriers related to limited sample size, lack of heterogeneity in the study populations to allow for adequate assessment of patient- and treatment-specific risks, and to overcome potential bias in study populations resulting from selection influences or incomplete follow-up.

- **New Partnerships:** the opening up of regional centers of excellence to interested participants in the field, from academic research institutions or elsewhere. In this way, the network hopes to

improve collaborations between academia and industry, e.g., SMEs, education, policy makers and the public health sector at large, which at present are largely excluded from academic networks.

- **Communication:** the establishment of communication and networks between previously isolated researchers in the same area of expertise creates the basis for longstanding relationship

Laying the groundwork for improved information, communication and education

Investment is also needed for improved information and communication services, thereby enhancing spread of excellence. This entails the technical and organizational foundation for an efficiently operating network, facilitated knowledge transfer and training opportunities, but also involves strengthened collaborative ties, easier accrual of clinical studies, better treatment standards and educational activities. The European Leukemia Network is ambitious to target besides traditional customers, i.e. physicians and patients, the many different groups in the society that may expect potential repercussions of network results for their own work including teachers, industry, health insurance companies, politicians, sponsors, cancer organizations, or the interested public.

5. POTENTIAL IMPACT

Leukemias constitute a paradigm for diagnosis and treatment of malignancy. From what has been shown, so far, leukemias have provided the first set of diseases of which effective molecularly targeted therapies highlight the value of elucidating the underlying pathogenetic defects ("proof of principle"). Successful targeted therapies include imatinib in CML and all-transretinoic acid and arsenic trioxide in APL.

To further explore this avenue of research further, a multidisciplinary team approach involving scientists in various fields of leukemia research, i.e. drug discovery, leukemia diagnostics, molecular genetics, clinical trials methodology, and biostatistics, is urgently needed. We propose the formation of a crosscutting **European treatment platform** for rapid clinical testing of novel drug candidates. This platform is ready for immediate implementation and reaches out to new partnership with the pharmaceutical industry, SMEs and smaller scale drug development consortia. The European Leukemia Network aims to set up appropriate biostatistical core facilities for support of clinical trials' activities in Europe. Employing validated intermediate endpoints and adapted statistical designs should help to arrive earlier and more reliably with conclusive results on toxicity and responses to given candidate drugs in phase I/II trials.

However, a potential limitation to clinical trials is the low incidence and molecular heterogeneity of leukemias in general that seriously hampers the quality of trials and leads to selection bias when evaluating studies with inadequately small sample size, incomplete follow-up or slow patient accrual. In order to study risk factor associations in the genomic era, prognosis, gene-environment interactions or genetically defined leukemic subtypes, assembly of large cohorts of subjects with balanced risk profiles is required. Resources should be allotted to the assessment of large cohorts with **data sets collected in a uniform fashion** for evaluation of markers of therapeutic interventions or survival. Scoring systems currently in clinical use need to be validated for imatinib or other targeted therapeutics.

By integrating the major leukemia study groups' **registries** information will be gathered on several thousands patients treated in various study protocols across Europe. The participating study groups commit themselves to a thorough longstanding follow-up. These data represent a unique source of information and would spread excellence far beyond the funding period. In general, **epidemiologic research** on leukemias has not been studied in a systematic fashion in Europe. Currently, data from regional registries exist on a limited and incomplete scale. Moreover, although some research has been conducted on treatment-related risks, very limited information is available regarding the potential impact of environmental exposures or gene environment interactions. Such an assessment would provide a better understanding of the roles of genetics and environmental exposure and interactions between the two. For instance, leukemia-associated chromosome aberrations occur in geographically heterogeneous distributions probably due to ethnic, genetic, socioeconomic and environmental factors. The identification of local leukemogenic factors in different parts of Europe could be achieved by the analysis of the geographical heterogeneity of leukemia-associated chromosome aberrations and the correlation with morphologic, immunologic, molecular genetic and treatment data. The spectrum of long-term outcomes that are in need for high-quality research include a thorough evaluation of long-term survivors, adverse effects of therapy such as secondary malignancies, organ dysfunctions, quality of life-, and quality of care assessments. Outcome issues are unknown for many populations, such as patients treated with novel therapies, those who may have unique genetic susceptibility traits, and those, for whom extended periods have elapsed since treatment.

Little is known about what patient populations will respond to **targeted therapies** or are at high risk for disease progression. However, this information is essential to the rational development and testing of intervention strategies. It is therefore perceived that the establishment of **data banks** containing large sets of clinical and laboratory data collected in a comprehensive and uniform fashion will specifically address the growing needs to better risk stratify patients in the genomic era, to optimize

conventional as well as emerging therapies and to overcome barriers related to limited sample size, lack of heterogeneity in the study populations to allow for adequate assessment of patient- and treatment-specific risks, and potential bias in study populations resulting from selection influences, such as incomplete follow-up. The proposed network will potentially be able to retrieve and exchange data information in excess of ten thousands of study patients. This should offer an unprecedented opportunity to achieve a **global leadership role in drug discovery** and **revolutionize standards** of care for leukemias in the advent of molecular targeted therapies and genomics as a powerful new research tool.

In current clinical practice, morphologic assessment, immunophenotypic analysis, and molecular cytogenetics are chiefly used to identify specific disease entities with the effect that molecularly distinct leukemia subentities are often lumped together. But more accurate diagnosis and new classification schemes are required to plan appropriate therapy and predict outcome. The challenge for the years ahead is to incorporate insights from gene array research into clinical practice., i.e. to rapidly migrate to a **molecular classification of leukemias**, which implies that ideally patients classified into the same subtype match in their pathogenesis so that the same molecular mechanisms lead to malignant transformation. This progress would be highly relevant for clinical practice as the course of disease and prognosis would be much more homogeneous. A major advantage of integrating leukemia study groups would be the capacity to accurately test and compare the „current“ classification with proposed „new“ classifications. A potential barrier for the validation of new classifications would certainly be the inadequate, incomplete collection and handling of data.

The new technology of gene expression profiling allows the simultaneous study of in excess of ten thousand different transcripts in normal and leukemic cells, thereby providing a powerful new diagnostic tool. While we are currently facing enormous complexities in terms of correctly interpreting gene expression analyses, a multitude of new opportunities open up for **exploiting genomic data in leukemias** that offer besides identifying candidate disease genes key information for drug discovery, toxicology and outcome research, risk and response stratification, classification of leukemias, or potential etiologic factors. Optimising currently applied leukemia diagnostics in terms of sensitivity, timing and reproducibility will increase prognostic information. This will enable the design of treatment protocols that reflect variations in leukemia biology, enable more informed decisions to be made concerning leukemia therapy in individual patients and is likely to lead to overall improvements in outcome for these diseases.

In conclusion, investment should be made in establishing an infrastructure that encompasses the major leukemia study groups in Europe. Prior investments have often focused on a single category or a limited group of leukemias and precursor conditions. The European Leukemia Network provides the **infrastructure** and the **critical mass** to overcome the widespread existing shortfalls currently facing leukemia research in Europe. There is a **need** for coordination and harmonization of treatment optimization studies, e.g. common control arm, exchange of study protocols, common study design, conditioning protocols or other transplant-related procedures. Furthermore, methodology in leukemia diagnostics, i.e. cytogenetics, morphology, immunophenotyping, and molecular genetics, lacks standardization and evaluation for quality control rounds. Different treatment strategies in a given field of leukemia are not comparable in terms of common data sets, which hampers future metaanalyses and validation of prognostic factors. No multi-national platforms exist for phase I and II drug development trials.

5.1 Contributions to standards

The network will contribute to the development of standards in the following areas:
Establishment of common data sets for clinical trials in

- CML (advanced stage of development)
- AML (initial stage of development)

- ALL, CLL, MDS, CMPD, common data sets needed and to be developed.

Standardization of diagnostics, quality control grounds
- Morphological diagnosis of peripheral blood and marrow cells
- Immunophenotyping
- Cytogenetic and molecular methods
- Detection of minimal residual disease
- Gene expression profiling technology

Standardization of therapeutic procedures
- Indications for stem cell transplantations (SCT) in the various leukemias
- Procedures in SCT, e.g. conditioning with reduced intensity procedures
- Anti-infection prophylaxis and treatment in neutropenic patients
- Diagnostics of fungal infections in neutropenic patients
- Standard operation procedures for development and evaluation of new drugs

Standardizations in leukemia diagnosis and treatment represent a **major objective of this network** and are detailed in 6.1.2.4.

The network will actively support existing and applicable international standards in the areas of IT, good clinical practice (ICH-GCP) and good epidemiology practice (GEP). EU regulations concerning privacy issues and IT ethics will be observed. Central Information and Communication Services will contribute to the development of new standards for IT issues related to diagnosis and treatment of leukemia in Europe. Furthermore, in co-operation with the Telematics Platform (TMF), a German organization committed to developing generic solutions in the area of telematics, as well as national and international organisations for standardization, standards in the field of telematics will be improved.

5.2 Contribution to policy developments

The European Leukemia Network is well aware of its **unique role as mediator of scientific knowledge and spread of excellence**, thereby reaching patients and individuals at the grass root level. The time is ripe to build the bridge between scientific discoveries and applications, crosscutting through all levels of society. Enhancing communication and information services will improve the access to state-of the-art leukemia treatments, improves medical decision-making, the quality of life of cancer patients and minimizes morbidity and health disparities among individuals. Patients suffering from leukemias are especially dependent on effective information and the need has even become greater with the advent of rapidly evolving scientific advances and potent molecular therapeutics at hands. For instance, recently, networking in Germany enabled that imatinib became available for a large number of CML patients in a short period of time. Leukemias are a heterogeneous groups of malignancies affecting a diverse patient population. Moreover, patterns of adverse effects vary greatly by disease and interventions, e.g., allogeneic stem cell transplantation. Finally, long-term survivors of leukemias have their own need for special information and coping strategies.

Besides offering all sorts of services on a sophisticated homepage the European Leukemia Network is ambitious to **disseminate state-of-the-art therapy into community practice**, publish findings in scientific journals and conferences. As the first step, standards for treatment approaches, methodology and leukemia diagnostics will be devised and published in major peer reviewed journals. The fact that virtually all European study groups participate in this network of excellence creates the common basis and reference point towards accomplishing this major task. But this will also serve as the springboard to reach influential health related organizations of society such as insurance companies, health policy

makers, medical societies, universities, teaching and training institutions to develop mutually acceptable strategies across Europe and to up-to-date educational and training curricula.

Thus, **representative key stake holders**, i.e., patient organizations, professional organizations, politicians, artists (e.g., the German network is proud to have won Mr. Jose Carreras and Mr. Rudi Völler, Manager of the German National Football Team) are already or will be invited to participate. They will make important contributions for overcoming existing fragmentation and national regulations. With regard to this new education/communication initiative the European Leukemia Network will seek advice and partnership not only with the NIH/NCI – these organizations are well advanced with cancer organization research – but even more importantly with other European cancer networks to align forces.

Following the proposed standards the European Leukemia Network will also seek to develop and implement **accreditation and certification of clinical trials and of physicians**, who achieved special knowledge, for instance in hematopoietic stem cell transplantation, channeling patients to specialized physicians and centers where state-of-the art treatments are offered. An immediately available **rotation and exchange program** for young scientists, i.e. students and junior faculty in dependent research positions, will create new and unforseeable career opportunities, will speed up knowledge and technology transfer and ultimately foster partnership and integration in European research. In the current practice, unfortunately, owing to better opportunities many young talents from Europe nowadays are directed away to research laboratories in United States. By offering flexible and methods-driven exchange programs on all levels of expertise the network will have a high integrative and educational impact.

By the proposed integrating activities the main goals of the European Leukemia Network are to intensify drug target discovery and validation, and clinical trials for leukemias, shorten drug development time, and lastly, improve standards of care and enhance spread of excellence in the advent of genomic medicine. This will have direct implications for the therapeutic progress by successful, large clinical trials, metaanalyses of specific subaspects, the elaboration of prognostic scores, recognition of gender specific differences, uniform data sets for study protocols, introduction of standards in molecular diagnostics, harmonization of transplant procedures, or the development of evidence based guidelines. While state-of-the-art leukemia therapy is becoming more and more complex, networking will offer synergism and efficient problem-solving capacities. Lastly, advances in understanding gained would be directly applicable to many other tumours.

5.3 Risk assessment and related communication strategy

There are no direct potential risks for society/citizens through the assembly of a European LeukemiaNet. Nevertheless, there are potential risks through testing of newly developed drugs in phase I/II trials for individual patients which are indeed a central initiative of the majority of the work packages. But these studies would be performed anyway by single centers and the potential risks are therefore in general not higher than they would be without the Network. In contrast, the main goals of the consortium are to reduce these risks by offering highly standardized and validated diagnostic and therapeutic procedures which are available for all participants throughout Europe by the central information system, the regular workshops and the Annual Scientific Meeting. This strategy also includes the rapid reporting of any severe adverse events to the lead participants and participants of the single work packages and the central services in order to facilitate the rapid and widespread knowledge of any negative experience through the worldwide web. No trial will be started without approval by the corresponding ethics committee.

6. OUTLINE JOINT PROGRAMME OF ACTIVITIES (JPA) FOR THE FULL DURATION OF THE PROJECT

6.1 Activities

The joint programme of activities consists of seven blocks of integration, jointly executed research and spreading of excellence activities and one block of scientific, technical and administrative management activities. The eight blocks of activities are:

1. **Establishment of the network structure by providing common information and communication structures.** These structures will be essential for networking both among clinical trial groups and interdisciplinary research and support groups.

2. **Set up of European networks for each leukemia and related syndrome.** These networks will comprise the national trial groups for each leukemia and represent the first stage of European integration.

3. **Set up of European platforms for each interdisciplinary specialty.** These platforms are subnetworks of excellence, of diagnostic, therapeutic and biometric research groups on their own and constitute the interdisciplinary partners enabling the clinical trial groups to achieve the high standard of patient care and research required for European leadership.

4. **Creation of clinical trial platforms for each leukemia for the conduction of clinical trials.** These platforms will provide transparency on ongoing studies, encourage recruitment of additional patients, increase visibility for the pharmaceutical industry and will provide the critical mass for European leadership and excellence.

5. **Set-up of a European Leukemia Registry.** A first step will be the establishment of uniform data sets and measures of quality control. Already existing national registries will be integrated.

6. **Standardization of diagnostic and therapeutic procedures**. All trial groups and their interdisciplinary partners will benefit from this activity concerning morphologic diagnosis, cytogenetics, detection of minimal residual disease, indications and procedures for stem cell transplantation, anti-infection measures, drug development and newly evolving diagnostic technologies such as gene expression profiling.

7. **Metaanalyses and evidence-based guidelines.** Metaanalyses and large randomized controlled trials will form the basis for the development of evidence-based guidelines. Guidelines as well as consensus reports and expert reviews will be instruments for all educational objectives and the spread of excellence.

8. **Scientific, technical and administrative management.** These activities will structure and monitor all activities of the network in order to achieve the proposal's goals and provide transparency for the sponsor.

These activities are broken down into 18 work packages, 17 of which comprise predominantly integration, jointly executed research and spreading of excellence activities (WP 2 – 17) and one predominantly management activities (WP 1) which, however, includes also strong integrative aspects. The partners participating in each workpackage are listed in 3.2. The partners participating in each activity (integrating, jointly executed research, spread of excellence, management) are listed in 10.1 and 10.2.

6.1.1 Integrating activities

Integrating activities will be the basis for a functioning European leukemia network. The following activities will promote integration of the leukemia trial groups and their interdisciplinary partners:

6.1.1.1 Establishment of the network structure by providing common information and communication structures

This will be carried out by the three central service projects: Network Management Center (NMC, WP 1), European Leukemia Information Center (ELIC, WP 2) and Central Information and Communication Services (CICS, WP 3). The following steps and activities will be performed immediately after activation of the proposal:

- Installation, operation and evaluation of central IT services supporting both the interaction of network participants and communications between the network and health care professionals, patients as well as the general public. A preliminary internet presence will be installed within the first month.

- Provision of communications facilities among network participants, to deliver expert information resources, to support continuous medical education for practitioners and specialized physicians in hospitals and to support clinical studies regarding patient recruitment, randomization and data management. Supply of services for patients which complement but do not replace the efforts of existing advocacy groups. In all cases the predominant medium will be the internet, in general and the world wide web, in particular. This will also contribute to the fundamental objective of creating a visible network identity.

- Set-up of a web-based registry of ongoing leukemia studies

- Set-up of an internet-based European meta-information system on diagnosis and treatment of leukemias as service institution of the network and for support of physicians and patients of all European countries. These activities will include: a) analysis of requirements for the European Leukemia Information Center, b) development of homepage structure and access modalities, c) development of information contents on network related topics, d) specific information for physicians, e) education, f) information letters, information for the public, g) information for staff of clinical studies, h) information for leukemia patients and relatives, i) quality control, j) information on gender related issues, k) cooperations with industry, European organizations (EHA, EBMT, ESH), EU-funded projects, such as the EHA-ECAH and the EurETAH projects, and similar international organizations such as National Cancer Institute (USA), Leukemia & Lymphoma Society (USA) and Leukemia Research Fund (UK).

- Development of a central web-based patient recruitment and randomization facility to support clinical trials performed or endorsed by the network. This deliverable is limited to the design, implementation and deployment of the facility.

- Telemedicine: development and operation of an exchange of image data for diagnostics (cytological, histological and cytogenetic images for quality assurance of diagnosis) and centralized DNA profile determination.

- Set up of an administrative infrastructure to foster integration, synergisms and communication within the network and with third parties. Organize a kick-off network symposium within the first month, annual follow-up symposia and six-monthly workshops of the trial and research groups. Promote conferences, training courses, newsletters, print media in close cooperation with WP 2

and 3 and networking via internet. This will facilitate knowledge transfer and spread of excellence.

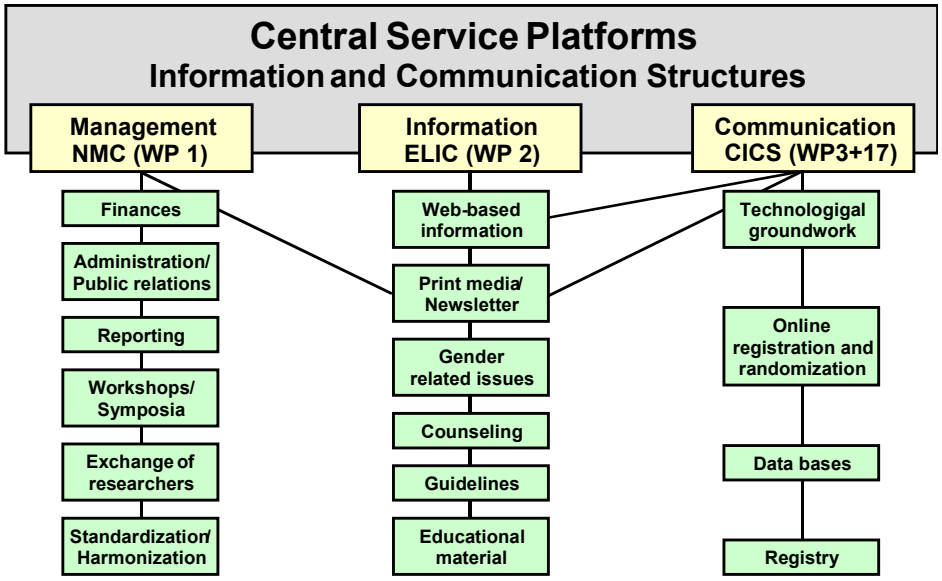

Fig. 3: Central Service Platforms: WP1, 2, 3 and 17 provide central services which are depicted here

Readily available information and communication structures are considered as a prerequisite for success and integration of the whole network. These activities are described in detail as listed in 6.1 of activities, above and represent the first tasks to be achieved for the function of the network. They will be carried out within WP 1 – 3: Network Management Center, Leukemia Information Center and Central Information and Communication Services.

WP 1 will set up and maintain the Network Management Center (NMC), the core project and administrative center of the network, and plays a pivotal role in integrating all WPs, participating centers and researchers to shape the networking structure. The task will be achieved by activities that increase information flow and communication, promote horizontal and vertical networking and create a spirit of mutual trust and cooperation.

Performance indicators WP 1 are:
- Number of participating trial groups, centers, researchers
- Kick off and annual symposia
- 6-monthly workshops of trial groups and interdisciplinary partners
- Collection and distribution of information on ongoing trials and research projects.

WP 2 will set up and maintain the European Leukemia Information Center (ELIC). A major issue is to develop information contents of high quality and general interest and to mediate communication processes within the network. The internet will be used as the main platform for information exchange. The main language will be English but part of the information, e.g. patient information, will be offered in several European languages. The Information Center supports major integrating aims of the network including improvement of collaboration, accrual of clinical studies, better treatment standards and education purposes. It links all groups involved in the field ranging from physicians, scientists, patients, relatives and the public. The following tasks will be performed:

- Analysis of requirements for an European Leukemia Information Center
- Development of homepage structures and access modalities
- Development of information contents for network related topics
- Information letters and information for the public
- Quality control of medical information on the internet by online questionnaires with the goal of a European certification

Performance indicators WP 2 are:
- Number of questionnaires and results
- Homepage contents, e.g. number of study groups, protocols for download, information offers for patients
- Number of registered website users
- Quality evaluation questionnaires
- Number of hits, visits and downloads
- Number of integrated cooperation partners
- Online user evaluation
- Quality evaluation of information contents

WP 3 will set up and maintain the Central Information and Communication Services (CICS). The following tasks will be performed:
- Creation of a communication platform for all network participants and for public relations
- Provision of the technological groundwork needed to integrate research activities
- Online registration and other services for participating researchers to support management
- As a start-up, survey to assess existing IT structures and the precise technological requirements for supporting the joint activities (e.g. joint clinical trials, expert groups) of network participants
- Design, develop, deploy and evaluate appropriate solutions (e.g. central patient randomization for clinical trials) in the areas of web-based communication, data management and telematics to support clinical trials and contribute to the spreading of excellence in this field

Performance indicators WP 3 are:
- Number of clinical studies supported
- Number of patients randomized in clinical studies
- Number and quality of papers published or presented based on then achieved research results of the network
- Number of visits at the homepage
- Number of persons in exchange programs
- Improvement of prognosis and quality of life patients

All three central service projects benefit from three years‘ experience in creating and successfully running a leukemia competence network across Germany integrating 29 research projects, 370 participating centers and more than 1300 network members. At a recent evaluation by an international group of referees the network was recommended for funding for two more years.

6.1.1.2 Clinical trial platforms (WP 4 – 9)

The set up of European platforms or subnetworks for each leukemia and related syndrome is the precondition for the creation of European clinical trial platforms and represents the first stage of European integration. The following steps and activities will be undertaken:
- Creation of organization structures with coordinator (=Lead participant) and own steering committee

- Information and communication platform within the central information and communication structure with
- Integrated own homepage in the internet
- Regular meetings (approximately every 6 months)
- Integration with the interdisciplinary diagnostic, therapeutic and biometric research groups

Thereafter these subnetworks will participate in the following joint integration, research and educational activities:

- Creation of clinical trial platforms
- Standardization of diagnostic and therapeutic procedures including stem cell transplantation
- Synchronization of phase III trials
- Set up of registries for each leukemia which together will constitute the European Leukemia Registry
- Promotion of diagnostic improvements
- Promotion of drug development
- Performance of metaanalyses and drawing up guidelines
- Organization of workshops, training courses and exchange of researchers

The creation of clinical trial platforms for each major leukemia or related syndrome across Europe will overcome European fragmentation and will provide the critical mass for European leadership and excellence in leukemia research and treatment. The following integrating activities will be performed by all or by single groups through networking with interdisciplinary partners:

Standardization

- Deployment of uniform common data sets across trials and European countries
- Develop standardized laboratory protocols and quality controlled procedures for
- Morphology/cytochemistry
- Immunophenotyping
- Cytogenetics and molecular genetics
- Evaluate residual disease
- Develop prognostic models

This process will be mediated by the specialized interdisciplinary working groups conducting WP 17 and WP 10 – 13. Already existing projects on harmonization and standardization of diagnostic procedures such as the EGIL project for immunophenotyping or the Biomed projects for evaluation of minimal residual disease will be integrated.

Overview on ongoing European studies

- Information on structure and trial activities of national trial groups through the internet
- Exchange of current trial protocols
- Information on participating centers and recruited patients

Common protocol standards

- Develop prognostic protocol standards for CML, AML, ALL, CLL, MDS, CMPD
- Harmonize patient selection and standardization of work-up at diagnosis

Harmonization of clinical trials

- Agreement on common protocol standards
- Harmonization of entry criteria
- Cross-study comparison of trials and prognostic models

Set up of a European leukemia registry for all clinical trial groups and partners
A registry will strengthen the integration process since it will provide information on incidence and disease patterns across Europe including gender, age and ethnic differences as well as familial aggregations. It also will allow the recognition of rare subentities, unusual courses of the various leukemias and information of prognostic relevance.

Set up of criteria for accreditation of clinical trials
Accreditation of all relevant leukemia trials across Europe

Performance indicators WP 4 – 9 are:
- Number of clinical trials started and/or completed
- Number of patients recruited into clinical trials
- Number of patients included into registries
- Improved predictive, prognostic or quality of life assessments
- Degree of harmonization of trials
- Number of SOPs and consensus papers
- Number of publications
- Number of meetings
- Number of meta-analyses
- Number of accredited trials

6.1.1.3 Platforms for each interdisciplinary specialty (diagnostic, therapeutic and biometric)

The set up of European platforms for each interdisciplinary specialty (diagnostic, therapeutic, biometric research) is the precondition for interdisciplinary high standard patient care and research. The following activities will establish the platforms:
- Creation of organization structures (same as trial networks)
- Information and communication structures with own homepage
- Regular meetings, provisionally every 4-6 months
- Integration with the clinical trial groups

The platforms will perform/participate the following integration, research and educational activities:
- Standardization of diagnostic and therapeutic procedures
- Set up, quality control and evaluation of registries
- Recognition of new targets, development of new drugs, clinical testing within clinical trial platforms
- Performance of metaanalyses and clinical guidelines
- Organization of workshops, training courses and exchange of researchers (same as for trial groups)

6.1.1.4 Development of diagnostic platforms (WP 10 – 13)

Close interaction of these platforms among each other and with the clinical trial platforms is the basis for research and networking of the diagnostic projects and for trial quality. None of the WPs can achieve its objectives without networking.

Standardization
- European reference panels (WP 10 – 13)
- Test inter observer concordance (WP 10)

- ISDN- or Web-based telemicroscopical consulting (WP 10, 11) – Gassmann, Rieder, Reith
- Internet forum for interdisciplinary discussion
- Quality control rounds (WP 10, 12)
- Cytogenetic website (WP 11)
- Discussion forum for difficult cases (WP 10, 11)
- Provide additional advanced methods (WP 11)
- Develop software for analyzing large cytogenetic data sets (WP 11)
- Standardize and develop robust sensitive assays (WP 12)
- Determine optimal timing schedules (WP 12)
- Develop standardized approaches to data analyses and reporting (WP 12)
- Develop software allowing to analyze large gene expression data sets in correlation with clinical data; development of consensus protocols for each genetic technique adapted to the different leukemias (WP 13)
- Develop standardized protocols and guidelines (WP 13)

Performance indicators WP 10 – 13 are:
- Establishment of European reference panels
- Organization of interdisciplinary consensus conferences
- Development of consensus protocols for the diagnostic work up of all types of leukemia and related syndromes
- Organization of quality control rounds
- Establishment of European telemicroscopical networks
- Set up of internet forum
- Training courses and improvement of teaching facilities with new technologies (WP 10)
- Number of rare abnormalities for which the prognostic impact could be clarified
- Number of new recurrent abnormalities identified
- Number of disease-specific aberrations identified
- Number and quality of publications within the network
- Number of researchers in exchange programs
- Implementation of technology transfer
- Number of difficult cases presented in the expert forum
- Number of new cooperations between network participants
- Improved techniques with better results (WP 11)
- RQ-PCR assays for rare fusion gene transcripts and for novel overexpressed genes (WP 12)
- Evaluation of validated RQ-PCR assays in national clinical trials (WP 12)
- Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report) (WP 12)
- Development of optimized sensitive validated assays for MRD detection (WP 11, 12)

Through their connection with the clinical trial groups, the diagnostic WPs are an integrating activity by themselves. They play an integrating role in the NOE as a whole.

6.1.1.5 Treatment research platforms (WP 14 – 16)

Integrating activities of these three platforms concern standardization and harmonization of treatment and laboratory research, protocols, data collection, exchange of materials, data and personnel.

Standardization
- Harmonization of indications for stem cell transplantation (WP 14)
- Standardization of procedures such as reduced intensity conditioning (WP 14)

- Evaluation and standardization of techniques to assess the risk for specific infections following antileukemic therapy (WP 15)
- Screening for invasive fungal infections and monitoring of antifungal therapy (WP 15, Einsele)
- Harmonization and quality assurance of new diagnostic procedures to detect pathogens (WP 15)
- Development of guidelines for scientific exchange between industry and academia (IP rights protection) (WP16)
- Development of data repositories for new targets, drugs, and the methodology for their preclinical evaluation
- Development of guidelines for clinical new drug evaluation with the aim to foster associated laboratory research programs, sample collection and identification of biomarkers

Data collection
- Expand survey on SCT in close cooperation with national transplantation registries and the EBMT for comparisons with the leukemia registry data and their quality control (WP 14, Gratwohl)

Exchange of materials and data
- Exchange of materials and methods to promote their availability (WP 14 – 18)
- Exchange of personnel for training and scientific exchange

Communication
- Develop and utilize an electronic information and communication platform (WP 16, Serve)
- Homepage with information on new compounds and their targets (WP 16, Serve)

Performance indicators WP 14 – 16 are:
- Number of clinical trials (WP 14)
- Number of patients recruited in studies (WP 14)
- Number of patients registered in the survey (WP 14)
- Number of metaanalyses (WP 14)
- Development of standardization and guidelines (WP 14, 15)
- Standardization and optimization of national guidelines to form European guidelines for anti-infection prophylaxis and therapy in neutropenic patients (WP 15)
- Definition of high-risk patients for certain infections (WP 15)
- Number of identified potential therapeutic targets (WP 16)
- Number of developed therapeutic compounds (WP 16)
- Number of tested biologically relevant substances (WP 16)
- Number of novel specific drugs transferred into clinical trials (WP 16)
- Number of publications based on the achieved research of researchers in exchange programs (WP 16)
- Number of meetings performed per year (WP 16)
- Durable technology transfer (WP 16)
- Continuous exchange of materials and knowledge (WP 16)
- Improved methods and methodology (WP 16)
- Improved prognosis and quality of life of patients (WP 16)

6.1.1.6 Platforms for biometry of registry, epidemiology, metaanalyses, prognosis and for guidelines (WP 17, 18)

These platforms will achieve the following integrative objectives:

Development of core data sets
A core data set is a list of variables, endpoints and definitions which are agreed upon and will be used in all therapeutic trials in a uniform manner. Core data sets are essential for a methodologically sound and valid comparative interpretation of research results and for metaanalyses which form an important basis for evidence-based medicine and guidelines. To achieve this, consensus meetings involving

-experts from almost all interdisciplinary workpackages and
-representatives from all leading trial and research groups across Europe have to be organized.

Thus, by this interaction and by the final product (i.e. the core data set) networking, integration and cooperation will be initiated and will persist**.**

Registries
Registries per se are scientific joint ventures which ask for long sustaining cooperation and integration of different professions and scientists across Europe. Data as specified in the core data sets will be received from many centers in Europe, there will be entry quality assurance procedures. WP 3 will provide the technical logistics. The statistical analyses will be done by WP 17 in close collaboration with the centers providing the data.

Prognostic models
Similarly, the development of prognostic models needs a very close integration of WP 17 with the clinical trials WPs. Once a prognostic model has been properly validated, close integration with WP 18 Guidelines and WP 2 and 3 Central Services will ensure and enforce implementation. The spectrum of integration activities includes

- personal meetings
- expert workshops and seminars and
- all types of communications.

Guidelines
A strong integrating motive is the establishment of a guidelines platform that establishes guidelines for diagnosis and treatment of all leukemias and related syndromes. This task will be accomplished in close collaboration between the clinical trial groups WP 4 – 9, the diagnostic groups WP 10 – 13 and the metaanalysis activity of WP 17.

Performance indicators WP 17, 18:
- Development of core data sets
- Number of clinical trials performed with standardized common data sets
- Number of guidelines
- Number of involved countries
- Number of involved/registered patients
- Number of involved hospitals and laboratories
- Number of studies registered within the network
- Number of SOPs/consensus protocols
- Number of clinical trials receiving biostatistical support
- Number of clinical trials started and/or completed
- Number of patients recruited or randomized in clinical trials or included into registries
- Degree of harmonization of trials methodology, minimal data sets, transplantation procedures
- Number and quality of publications of joined research activities

6.1.2 Programme for jointly executed research activities

6.1.2.1 Clinical trials

The integration of the leading leukemia trial groups across Europe will enable the conduction of cooperative trials even on rare subentities of the leukemias and related syndromes. By the use of standardized data sets and common guidelines for the conduction of phase I/II trials, trial quality will be of high standards and the outcomes will be comparable across Europe. Through the transparency and visibility of the clinical trials platform and the availability of large patient numbers, the transition time from drug discovery to its application at the bedside will be significantly shortened. The network will encourage participation in trials and acceptance of clinical research.

Creation of clinical trial platforms for each leukemia and related syndrome for the conduction of clinical trials. Their establishment requires the availability of the central management, information and communication structures described in blocks 1-3, which have to be set up first.
Activities and networking of clinical trials platforms are illustrated inFigs. 4 and 5

The following common activities will establish the clinical trials platform:

- Provision of uniform common data sets for all trial groups
- Information on structure and trial activities of national leukemia trial groups
- Internet based registry of ongoing trials
- Exchange of current trial protocols
- Information on number of participating centers and recruitment activities
- Conduction of specific therapeutic trials for the various leukemias and related conditions
- Analysis of gender specific differences
- Organization of training courses, trial meetings and exchange of researchers

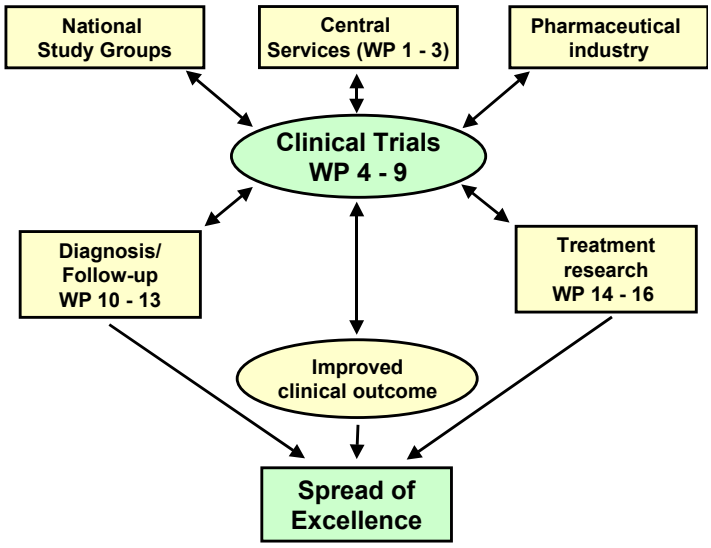

Fig. 4: Activities of clinical trials platforms

Trial activities are for **CML (WP 4)**:

- Harmonize entry and follow-up criteria (EI-CML)
- Study combinations of imatinib with IFN or AraC in chronic phase CML (German, French, UK groups)
- Conduct phase II trial with combination of imatinib and pegylated IFN alpha (German, Italian, UK, Nordic groups)
- Conduct phase I/II trials with farnesyltransferase inhibitors, homoharringtonine, decitabine, arsenic trioxide, arsenictrioxide, arabinosylcytosine and YNKO1 (German, UK, French, Irish, Greek, HOVON and Italian groups)
- Study high-dose imatinib as first line treatment of high risk chronic phase CML (Italian and Nordic groups)
- Monitor cytogenetic and molecular response in low and intermediate risk chronic phase CML patients treated with standard dose imatinib (Italian and German groups)
- Study low-dose interferon alpha to improve the molecular response in imatinib responsive patients with chronic phase CML (Italian, German, Swiss, Nordic groups)
- Apply and evaluate new pharmacokinetic and pharmacodynamic methods for guiding phase I/II anticancer drug development (Danish and Swedish groups, Haferlach)
- Study consecutive versus parallel imatinib/interferon alpha combinations (German group)
- Study FLT3 and VEGFR inhibitors as single agents or combined with imatinib in imatinib refractory patients (Italian group)
- Conduct dose ranging phase I/II study of imatinib in combination with cytarabine (HOVON)
- Investigate the effects of imatinib on the pharmacokinetics of dextromorphan in a cross over study (Belgian group)
- Study the place of stem cell transplantation (SCT) in the decision tree for treatment of CML (German, Swiss groups)
- Evaluate the optimal timing for harvest of hematopoietic blood stem cells during imatinib treatment for performing autologous SCT in imatinib refractory patients as alternative to allogeneic SCT (Danish and Swedish groups, Haferlach)
- Analyze gender specific differences (Metaanalysis, Berger/Hasford)

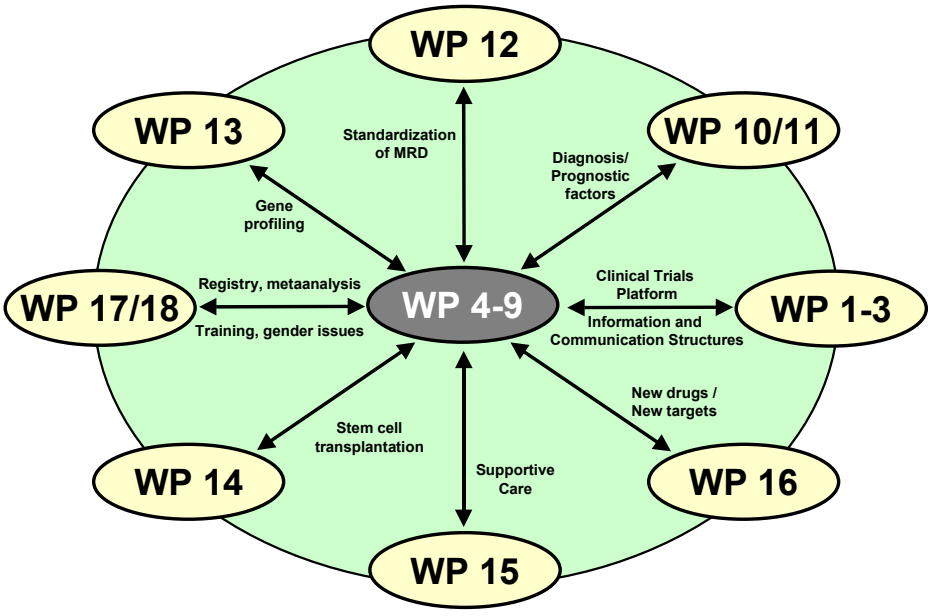

Fig. 5: Networking of the clinical trial platforms (WP 4-9)

for **AML (WP 5)**

- Adopt new common protocol standards (NCI, EU)
- Harmonize entry criteria and patient selection
- Implement networking instruments such as upfront randomization
- Develop a common standard arm to facilitate cross trial comparison and validation of treatments
- Validate and compare antileukemic effects at a molecular level between different therapeutic regimens of different trials
- Optimize therapeutic regimens according to their antileukemic effects at a molecular level
- Elucidate the predictivity of relapse on the basis of molecular MRD monitoring
- Incorporate MRD guided therapy into trials
- Compare MRD guided therapies across trials
- Compare different intensity chemotherapy in addition to ATRA in APL across trials using networking instruments
- Validate the role of arsenic trioxide in APL by cross trial analysis
- Validate and compare therapeutic regimens for APL on the basis of molecular MRD
- Investigate the role of reduced intensity stem cell transplantation in older patients
- Analyze gender specific differences in the incidence of AML subtypes and in the relative value of treatment alternatives

for **ALL (WP 6)**

- Cross-study evaluation of prognostic models
- Cooperative development of risk stratified treatment based on MRD
- Evalute new prognostic markers evolving from cytogenetics, molecular genetics and microarray technology
- Synchronize standards of phase III studies to achieve comparability
- Metaanalysis of rare subtypes e.g. cytogenetic subgroups, adolescents or treatment approaches autologous SCT, non-myeloablative SCT
- Analyse gender-specific differences
- Phase III intergroup studies in rare subtypes of ALL e.g. mature B-ALL, in elderly ALL patients
- Phase II-III studies with monoclonal antibodies e.g. antiCD20, antiCD52, antiCD22
- Phase II studies with new cytostatic drugs in relapsed/refractory ALL
- Phase II studies with Imatinib in Ph/BCR-ABL+ ALL
- Phase II studies with new molecular drugs
- Phase II studies with new approaches for stem cell transplantation e.g. dose reduced transplantation, cell therapy

for **CLL (WP 7)**

- Conduct phase I/II trial with new anti-CD23-antibody (Hallek)
- Conduct phase I/II trial with antisense oligonucleotides (Hallek)
- Conduct phase I/II trial with the combination of fludarabine, cyclophosphamide and rituximab (German, French study groups)
- Conduct phase I/II trial with the combination of fludarabine and alemtuzumab (Italian, UK, German study groups)
- Conduct clinical trials to determine the role of bendamustine (European study group)
- Conduct clinical phase I/II trials with CLL vaccine (Hallek)
- Conduct phase I/II trials with the combination of fludarabine and erythropoietin as supportive treatment in patients with relevant comorbidity (German CLL group)
- Define markers for predicting cytogenetic and molecular response to chemo-immunotherapy or other therapeutic modalities (Hallek)
- Determine indications for SCT in CLL (European study group)

- Monitor the molecular response after chemo-immunotherapy by real time quantitative PCR and four color flow cytometry (UK, German, Spanish and French study groups)
- Conduct phase I/II trials to evaluate the immunotherapy with monoclonal antibodies and cytokines (Hallek)

for **MDS (WP 8)**

- Conduct phase I/II trial with 5-azacytidine (Fenaux, Avicenne, Hellström-Lindberg, Nordic MDS, Dundee MDS study groups)
- Conduct phase I/II trial with thalidomide (Ganser)
- Conduct phase I/II trial with farnesyltransferase inhibitors (Fenaux, Ortho-Biotech)
- Conduct phase I/II trial with new antiangiogenic drugs in 5q- syndrome (Aul)
- Conduct phase I/II trial with arsenic trioxide (Fenaux)
- Conduct phase I/II trial with FLAG-IDA intensive chemotherapy followed by autologous HSCT in high risk MDS (Sanz, PETHEMA)
- Conduct phase I/II trial with intensive chemotherapy with or without a mdr reverting agent (Fenaux)
- Conduct phase I/II trial with intensive therapy combined with CD33 conjugates – myelotarg (de Witte, Dundee MDS, EORTC study groups)
- Conduct phase I/II trial with rabbit ATG plus cyclosporine A in low risk MDS (Passweg, Swiss study group)
- Study maintenance treatment with 5-azacytidine in elderly patients with MDS with assessment of methylation status of CD34 + cells (Hellström-Lindberg (Nordic MDS), PETHEMA study groups)
- Study the effect of darbepoietin on the anemia of MDS (Hellström-Lindberg (Nordic MDS))
- Study new forms of SCT in high risk patients (Martino – GETH, Gluckman – Paris, de Witte – EBMT, Kröger – Hamburg)
- Analyze gender specific differences (Bowen)

for **CMPD (WP 9)**

- Conduct phase I/II trial with tyrosine kinase inhibitors (German group, Lengfelder), farnesyl transferase inhibitors, proteasome inhibitors, anti FLT3 and anti-VEGF agents (Barbui, Barosi).
- Set up and validate a new severity score (P. Bernasconi, Barosi)
- Study biomarkers for disease progression, survival etc. in the light of gene array data
- Perform randomized comparison of low-dose thalidomide plus prednisone versus hydroxyurea plus prednisone in myelofibrosis with myeloid metaplasia
- Perform randomized comparison of imatinib mesylate versus no treatment in low risk PV patients
- Study the role of SCT in high risk patients

The **clinical trials platform** will use drugs provided by pharmaceutical companies and/or by the expert group on treatment research/new targets/new drugs (WP 16).
Close cooperations exist with the pharmaceutical companies

- Amgen
- Chugai
- Gilead Sciences GmbH
- Hoffmann-LaRoche
- ILEX Oncology
- MedacSchering Onkologie
- Merck
- Novartis

- Ortho – Biotech
- Pharmacia
- Pharmion
- Ribosepharm
- Aventis-Synthelabo
- Schering-Plough / Essex Pharma
- Wyeth
- and others.

The transparency created by the platform will prevent unnecessary duplication of studies, will create additional visibility and will require lean management due to use of common network services. For all clinical trials the observation of the Declaration of Helsinki and the rules of Good Medical Practice is standard.

6.1.2.2 Prognostic and epidemiological research

Through the data registered from clinical trial groups and diagnostic platforms to the central registry a wealth of information is available that can be used to answer a variety of important epidemiological and prognostic questions.

An essential first step to a qualitatively satisfactory analysis is the establishment of core data sets by the expert group of WP 17 in close cooperation with the clinical trial groups.

The sequence of activities is the following:
- Registry of patients from current trials
- Identification of all prospective leukemia studies in Europe since 1990
- Data collection from these studies
- Prognostic model analysis
- Quality control of data

European Leukemia Registry. A European registry involves clinical and interdisciplinary groups and will strengthen the integration process. The registry will address a number of important research topics in the fields of epidemiology, pathobiology and prognosis such as the determination of incidence and disease patterns across Europe including gender, age and ethnic differences as well as familial aggregations, overlap syndromes or precursor conditions. This approach will enable conclusions to be drawn regarding the courses of disease in relation to prognostic markers or treatment response.

The following groups will register patients and data:
- Clinical trial groups (WP 4 – 9) with links to Swedish, Finnish CML registries, German, Austrian MDS registries, Italian MDS registry (C. Bernasconi), Spanish MDS group, French Avicenne MDS group, Dundee Clinical Database, Southeast MDS Registry Netherlands and others
- Diagnostics group (WP 10, Béné)
- Cytogenetics group (WP 11)
- Gene profiling group (WP 13)
- Transplantation expert group (WP 14)

The registration process will start after
- Establishment of central communication structures
- Introduction of standardized uniform data sets

National web-based registries are operating, or under construction, in several European countries such as national and European leukemia and transplantation registries (EBMT, Scandinavian and Italian

registries, regional registries). Through integration of these registries, the collection of large numbers of selected and validated data for the European registry will be enhanced. By comprising all major leukemia study groups, the registry will have a high integration potential. The JPA plans a registry of all patients recruited by the European leukemia study groups. It will promote standardization of diagnostics and management including transplantation procedures and of methods for detection of biological prognostic factors, MRD quantification and gene profiling. The program will foster metaanalyses of previous and ongoing randomized trials and the development of evidence-based guidelines. These activities will be led by WP 17 Registry and carried out by networking with the expert groups of WP 3 Telematics, WP 11 Cytogenetics, WP 12 MRD, WP 13 Gene Profiling, WP 14 SCT, WP 16 Treatment Research/New Targets/New Drugs and WP 18 Guidelines Platform. By integrating these interdisciplinary expert groups with the clinical trial groups into a coherent network, a high degree of integration will be reached in leukemia research and treatment across Europe.

Monitoring, quality control and evaluation of the registry will be carried out by the biometric expert group of WP 17 in close cooperation with the clinical trial groups (WP 4 – 9) and the cytogenetics and transplantation groups (WP 11, 14). Networking through the registry is illustrated in Fig. 6

Patients data protection will be observed in all instances according to European and national legislation.

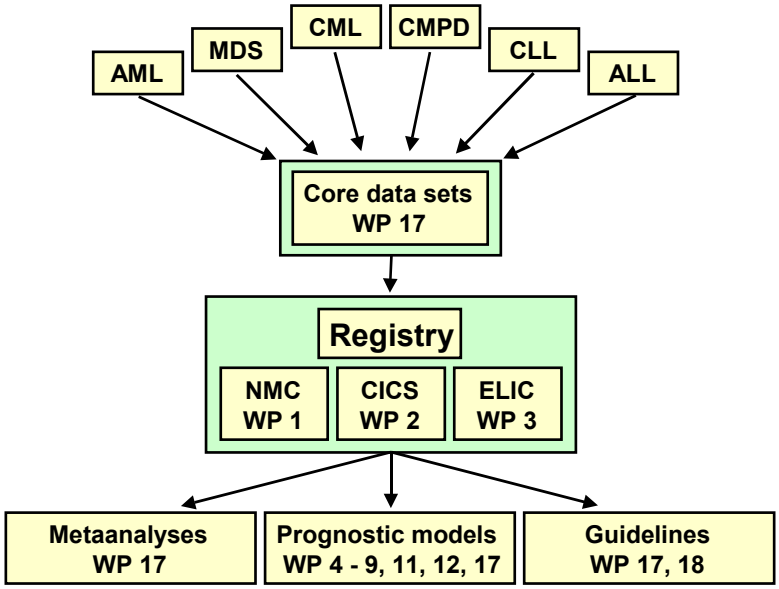

Fig. 6: Registry

The registry can assist the study groups (WP 4-9) with the following tasks:

Epidemiology and risk factor analysis

- Study incidence and geographical distribution in Europe
- Study ethnicity, gender, age differences with respect to clinical manifestations, treatment response and outcome
- Study pathogenic correlations with other malignancies
- Study familial aggregates
- Study environmental exposures as link to causation
- Determine proportion of patients in individual countries treated on specific protocols or with specific therapies, e.g. SCT

Predictors of survival and treatment response
- Study new prognostic markers for disease progression and survival in the light of gene array data
- Evaluate intermediate endpoints such as molecular responses for high-dose and combination therapy
- Analyze complete molecular remissions within the different treatment modalities
- Compare conventional staging systems with molecular-based classification systems
- Propose and validate new prognostic staging systems on clinical, biological and genetic parameters

Outcome analysis
- Correlate quality of treatment responses with survival times
- Long term follow-up of patients with molecular responses
- Compare short and long term adverse effects of high-dose and combination therapies
- Influence of pretransplant therapies on the outcome of allografting in cooperation with EBMT registry

Benefits of a Europe-wide leukemia registry are clear cut:
- Sufficiently large sample size collected from all over Europe that ensures demographic diversity and heterogeneity of disease characteristics and treatment exposures
- Uniform collection of data
- Utilization of extremely well defined outcomes
- Collection of genomic data to facilitate the evaluation of molecular genetic factors
- Appropriate support (e.g. by biostatistics, data processing, and survey research)
- Through establishing a bank of biologic material (e.g., CML cells) perform prospective and retrospective studies, the biological material will be stored and be available to the central registry (or national biobanks). It could be used for studies on cell biology, cytostatic drug resistance, cytogenetics, molecular biology, etc.

Future investigations will be performed in each of four distinct areas
- Identification and characterization of patients with high risk profiles
- Correlation with the biological basis of identified risk associations utilizing gene array analyses
- Definition of prognostic markers for predicting hematologic, cytogenetic and molecular responses to the various therapeutic modalities and survival.
- Develop and apply new tumor models and concepts for preclinical identification of new pharmacological principles for clinical development.

6.1.2.3 Diagnostic research

Development of agreed rules for developing a pan-network of cytogenetic data with clinical outcome
- Correlation of cytogenetic data with clinical outcome

Gene expression profiling in leukemia.
Main objectives of **global gene expression analyses** are:
- Improvement of diagnostic accuracy and reliability
- Identification of prognostic markers and the prediction of treatment outcome
- Definition of new therapeutic targets at the molecular level
- New insights into the biology of leukemias
- Close cooperation of different specialist groups in Europe comprising basic researchers, clinical scientists, clinical trial groups and biostatisticians as integrated in this network

- Global gene expression analyses with microarrays as first applied in ALL with practical applications for prediction of response, identification of subgroups and prognostic factors.
- Confirmation and extension of conventional leukemia (AML) diagnosis according to FAB criteria

Research activities jointly executed with clinical trial groups will be:
- Identification of new molecular targets by analyzing large gene expression data bases
- Identification and analysis of new leukemia subtypes on the basis of gene expression profiling
- Collection of gene expression data on rare abnormalities
- Design and development of genomic microarrays for the detection of disease-specific chromosomal imbalances

Establishment of novel molecular targets for MRD detection
This research will be led by the MRD group (WP12). The following steps will be taken:
- Design and testing of novel fusion gene assays, e.g. to detect DEK-CAN, MLL-AF6, MLL-AF9, MLL-AF10, NPM-MLF1 associated with AML and
- To detect PDGFR-A and –B fusions, namely FIP1L1-PDGFRA, ETV6-PDGFRB and H4-PDGFRB in chronic myeloproliferative disorders (WP 9)
- Identification of targets for MRD detection in leukemias lacking fusion genes generated by chromosomal translocations by assays for genes commonly overexpressed in acute leukemia including WT1, EVI-1 and PRAME.
- Achievement of standardization in these MRD analyses
- Implementation of MRD assessment in the clinical setting

Development of new diagnostic techniques for prognostic models of various therapeutic approaches
New techniques in development for this objective are
- FISH including multicolor FISH
- Comparative genomic hybridization
- Flow cytometry, immunophenotyping using 5 parameter 3 color flow cytometry
- Clonal analyses of hematopoietic precursors by X chromosome inactivation patterns (e.g., HUMARA assay)
- Gene expression profiling by cDNA microarrays
- Protein expression profiles using surface enhanced laser desorption ionization and time of flight mass spectroscopy
- All MDS cases undergo cytomorphological, cytochemical, immunophenotypical and cell cycle diagnosis as well as conventional karyotyping
- The role of autoreactive T-cell clones will be explored. Studying the alteration of T-cell receptor Vß repertoire before and after treatment with immunesuppression
- T-cell spectrotyping is performed according to standard procedures
- Coculture of hematopoietic progenitor cells with autologous T-cells to analyze autoactivity of T-cells

6.1.2.4 Standardization of diagnostics and therapy

Standardized and quality controlled diagnostic procedures and therapies are of utmost importance for good patient care and constitute the basis for successful treatment and for improvements in outcome. Standardization will be achieved for
- Morphological diagnosis of peripheral blood and bone marrow cells (WP 10, Orfao, Gassmann, Béné)
- Immunophenotyping (WP 10, Ludwig)
- Cytogenetic and molecular methods (WP 11, Fonatsch)

- Detection of minimal residual disease (WP 12, Grimwade) and,
- In particular, for the new gene expression profiling technology with gene chips (WP 13, Haferlach).

Standardizations are also essential for therapeutic procedures such as:
- Stem cell transplantation, (WP 14, Niederwieser)
- Anti-infection prophylaxis and treatment in neutropenic patients (WP 15, Ljungman) and
- Standard Operation Procedures (SOPs) for development and evaluation of new drugs (WP 16, Serve)

All standardizations will be performed in the context of the patient management by the clinical trial groups (WP 4-9). Integration of standardization is illustrated in Fig. 7

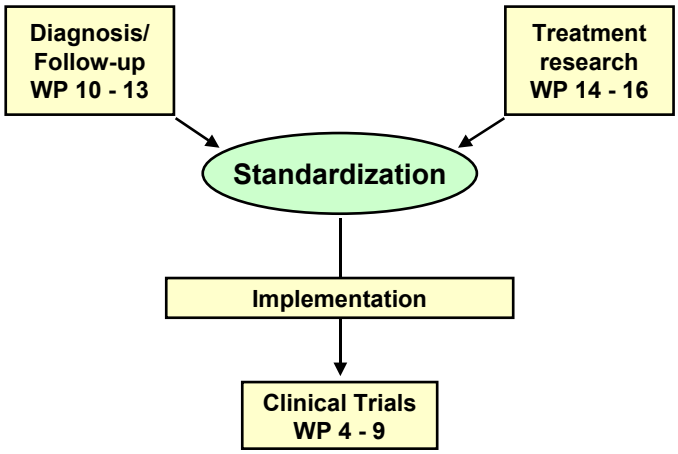

Fig. 7: Integration of Standardization

In detail, the following tasks will be performed:

Morphologic diagnosis (WP 10)
- Establish a European reference panel for diagnostics (Gassmann)
- Test inter-observer concordance (Gassmann)
- Set up ISDN-based telemicroscopical consulting and discussion forum (Orfao)
- Set up Internet forum for interdisciplinary discussion of difficult cases
- Organize morphological and immunological quality control rounds for specialized laboratories
- Establish improved teaching facilities in the light of new technologies (Gassmann)
- Set up of a European slide and multimedia bank for educational purposes (Gassmann)

Cytogenetics (WP 11)
- Facilitate cooperation – cytogenetics website (Hagemeijer, Mitelman, Rieder, Schoch)
- Establish a forum to present difficult cases (Mecucci, Knuutila, Pedersen-Bjergaard, Fonatsch)
- Provide additional methods (24 color FISH, CGH, telomere FISH, etc.) and quality control (Grimwade, Jotterand, Schlegelberger, Dastugue)
- Develop a software for analyses of large cytogenetic data sets in correlation with clinical data and other diagnostic information (Hagemeijer, Johansson, Rieder, Huret)
- Arrange ISDN- and web-based telemicroscopical discussions linked to morphologists (Hagemeijer, Mitelman, Rieder, Schoch)
- Identify new recurring chromosome aberrations by analyzing large cytogenetic data bases (Dastugue, Mecucci, Fonatsch, Rocci)

- Identify and analyze cryptic and complex chromosome aberrations by using multicolor karyotyping (Dastugue, Mecucci, Fonatsch, Rocci)
- Collect data on rare abnormalities (Mitelman, Romana, Harbott, Andersen)
- Define subcommittees for the organization of workshops on actual topics, technical workshops, training and exchange programs, development of standardized protocols and guidelines. (Grimwade, Haas, Rocchi, Schoch)

Minimal residual disease (WP 12)

- Standardize and develop robust, sensitive assays in the context of internal and external quality assessment
- Determine optimal timing schedules for MRD assessment
- Develop standardized approaches to data analysis and reporting of MRD data, coupled with the development of standardized formats for reporting of RQ-PCR data
- Design and test novel fusion gene assays associated with AML
- Characterize molecularly BCR-ABL-negative myeloproliferative disorders (WP 9)
- Identify targets for MRD detection in leukemias lacking fusion genes generated by chromosomal translocations, e.g. WT1, EVI-1 and PRAME
- Implement MRD assessment in the clinical setting using standardized RQ-PCR approaches in the context of large scale national clinical trials, e.g. MRD assessment for CBFbeta-MYH11 and AML 1-ETO fusion transcripts
- Implement MRD assessment to evaluate novel agents
- Disseminate established and validated standard approaches to MRD assessment through the information center
- Facilitate exchange of laboratory scientists between participating laboratories

The program of the MRD-workpackage is illustrated in Fig. 8

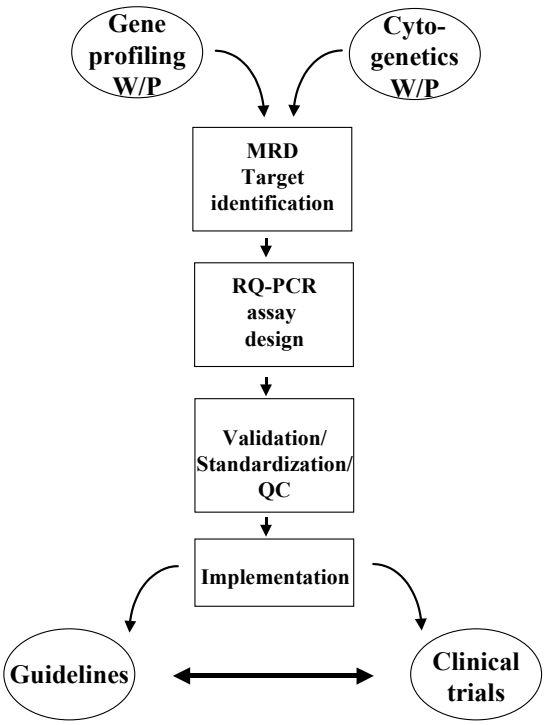

Fig. 8: Program of the WP 12 MRD

Gene profiling (WP 13)

- Develop software allowing analysis of large gene expression data sets in correlation with clinical data and other diagnostic information
- Identify new molecular targets by analyzing large gene expression data bases
- Facilitate exchange of personnel among the participating institutions for defined training programs
- Exchange information about research projects among the members of the WP and the availability of materials (for standardization activities) through network internet page
- Develop consensus protocols for each genetic technique adapted to the different diseases
- Establish a forum of experts to discuss difficult cases
- Organize workshops presenting „state-of-the-art“ diagnostics and therapeutic implications for the different leukemia subtypes
- Develop standardized protocols and guidelines

6.1.2.5 Treatment Research

Transplantation (WP 14)

Stem cell transplantation (SCT) and imatinib or immuno-chemotherapy are currently the most powerful therapies for patients with chronic leukemias. They are complementary, not exclusive and probably synergistic. Both are high cost therapies

- Harmonize indications for stem cell transplantation in an era of new alternatives for successful drug treatment (Ispizua)
- Standardize procedures in particular conditioning procedures with reduced intensity across Europe (Niederwieser)
- Expand the EBMT survey of transplantation activities in Europe allowing study of indications and procedures across Europe in a timely fashion (Gratwohl)
- Exchange information on cure rates with non-transplant and transplant procedures (Apperley)
- Determine optimal treatment strategies (Bacigalupo)
- Assess risk profiles and outcome utilizing retrospective and prospective analyzes of trial groups (Gratwohl)
- Integrate SCT into all disease specific trials in a prospective standardized way in order to determine its respective value (Apperley)

Supportive care/anti-infection prophylaxis and treatment (WP 15)

- Evaluate new diagnostic assays and recommendations for their application in patient care (Ward, Buchheidt)
- Evaluate and standardize techniques to assess the risk for specific infections following antileukemic therapy (Martino, Ullmann)
- Evaluate and standardize screening for invasive fungal infections and monitoring of antifungal therapy (Maertens, Maschmeier)
- Harmonize and control quality of new diagnostic procedures to detect pathogens and pathogen specific immunoresponses (Einsele, Ljungman)
- Establish a platform for the collection of samples for analyzes of genetic susceptibility to certain infections (Einsele, Cordonnier)
- Implement a refined monitoring protocol of pathogen- specific immunoresponses (Ljungman, Reusser)
- Study and standardize antimicrobial prophylaxis (Locasciulli, Engelhard)
- Devise recommendations for risk assessment of antimicrobial prophylaxis and treatment (Viscoli, Engelhard)
- Evaluate the role of reverse isolation procedure on infectious complications (Akan, Dekker)

Treatment research, new targets, new drugs (WP 16)
Develop standards and guidelines for early clinical trials including protocols for phase I/II trials and testing the new drugs in the networking study groups (WP 16).

Recognition of new targets for new drugs
The main objective of this network research activity is to enhance the development of new treatment options for leukemia and related syndromes and transfer these into clinical trials. The following program for jointly executed research activities will be carried out:
Definition of molecular targets (WP 13):
- Identification of potential targets based on genomics and proteomics

Development of new compounds (pharmaceutical industry, WP 16)**:**
- Inhibitors of identified potential targets, e.g. in high throughput screens
- Differentiating agents, e.g. HDAC inhibitors

Testing the biological relevance of targets and preclinical efficacy of compounds:
- In vitro testing in cell culture models
- In vivo testing in animal models for leukemias
- Identification of drug synergism

Development of surrogate markers for clinical trials (basic scientists and clinical trial groups)**:**
- Development of methodology to verify target inhibition
- Development and application of assays to analyze pharmacokinetic/pharmacodynamic relationships in clinical trials
- Fostering of laboratory research programs associated with clinical trials
- Assessment of biological effects of targeted drug application in patients

Performance of "First in men" testing (clinicians and clinical trial groups)

6.1.3 Spreading of excellence activities

Activities to spread excellence are part of all WPs **(education, training courses, exchange of researchers, PR-activities etc.)** and are detailed there. A special central service WP (European Leukemia Information Center, WP 2) has been set up to promote spread of excellence with the help of WP 1 and 3. In addition, spreading of excellence is a major activity of the guidelines platform (WP 18). The activities comprise the following components:

- Internet-based information on ongoing studies, standards for diagnosis and treatment and education programs (WP 2) to
  - Ease communication
  - Create a virtual center of excellence
  - Inform patients and the public about activities of the network
- Training programs (WP 1)
  - Exchange program for personnel including staff of clinical studies
  - Training programs for researchers and physicians
- Guidelines (WP 18)
  - Development of evidence-based guidelines for diagnosis and treatment of the leukemias, their subgroups and related syndromes
- Presentation of the network (WP 1, WP 2)
  - Regular meetings of network members for exchange of results and dissemination of achieved knowledge
  - Reports on network and achievements at national and international meetings
  - Publications
- Open network structure

- Inclusion of additional network participants from European countries – including Eastern Europe – by open network structures

The spread of excellence by the network is illustrated in Fig. 9.

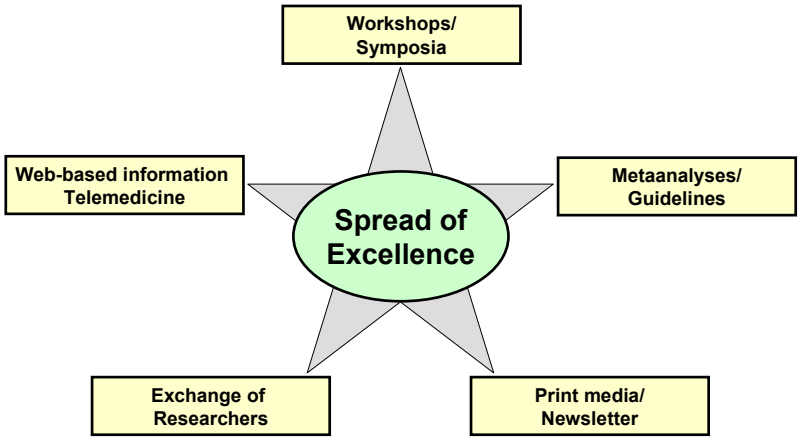

Fig. 9: Spread of excellence, metaanalyses/guidelines, education

Finally, the mere fact that virtually all major leukemia trial groups and their interdisciplinary partners representing more than 1000 participating centers and ten thousands of patients in 22 countries are part of the network is an important factor contributing to the spread of excellence across Europe on all levels including the Eastern European countries.

Metaanalyses and guidelines. The performance of metaanalyses of randomized controlled trials (RCT) provides the basis for evidence-based guidelines and is of utmost importance for setting standards for patient management and for training. Metaanalyses, consensus reports, expert reviews and guidelines will be prepared by specialists from clinical trial groups in close cooperation with experts from WP 17 and 18. The following tasks will be perfomed:

- Update of metaanalyses on randomized studies with interferon α in CML (WP 4, WP 17, Hasford, Porkka)
- Metaanalyses on randomized studies in AML (WP 4, WP 17, Hasford, Porkka)
- Metanalyses on biological characteristics and specific subgroups in ALL (WP 6, WP 17, Messerer)
- Consensus reports and expert reviews when no randomized studies are available.
- Guidelines will be established for all leukemias and related syndromes in close cooperation with the lead participants of the trial groups (WP 18).
- Guidelines will be established for all standardizations of the diagnostic and therapeutic procedures standardized in WP 10 – 16, 18.
- The propagation of the guidelines will be performed by the Network Information Center (WP 2)

6.1.4 Management activities

The NOE comprises 18 workpackages, WP 1 concentrating on scientific, technical and administrative management and each of the other workpackages (WP 2 – 18) representing a network across Europe on its own. Each workpackage contributes to integrating activities, jointly executed research activities, activities to spread excellence and management activities.

An overview of the network management activities is presented in Fig. 10.

The following management activities are foreseen:

6.1.4.1 Scientific management

Workpackage level
Each workpackage is managed by one or more (up to 7) lead participants (LP) and a WP steering committee (WP-SC) analogous to the steering committee (SC) for the entire network. The WP-steering committees consist of the coordinators of the respective national trial groups or laboratories involved in the WPs. Each WP contributes to the joint program of activities according to the program outlined above.

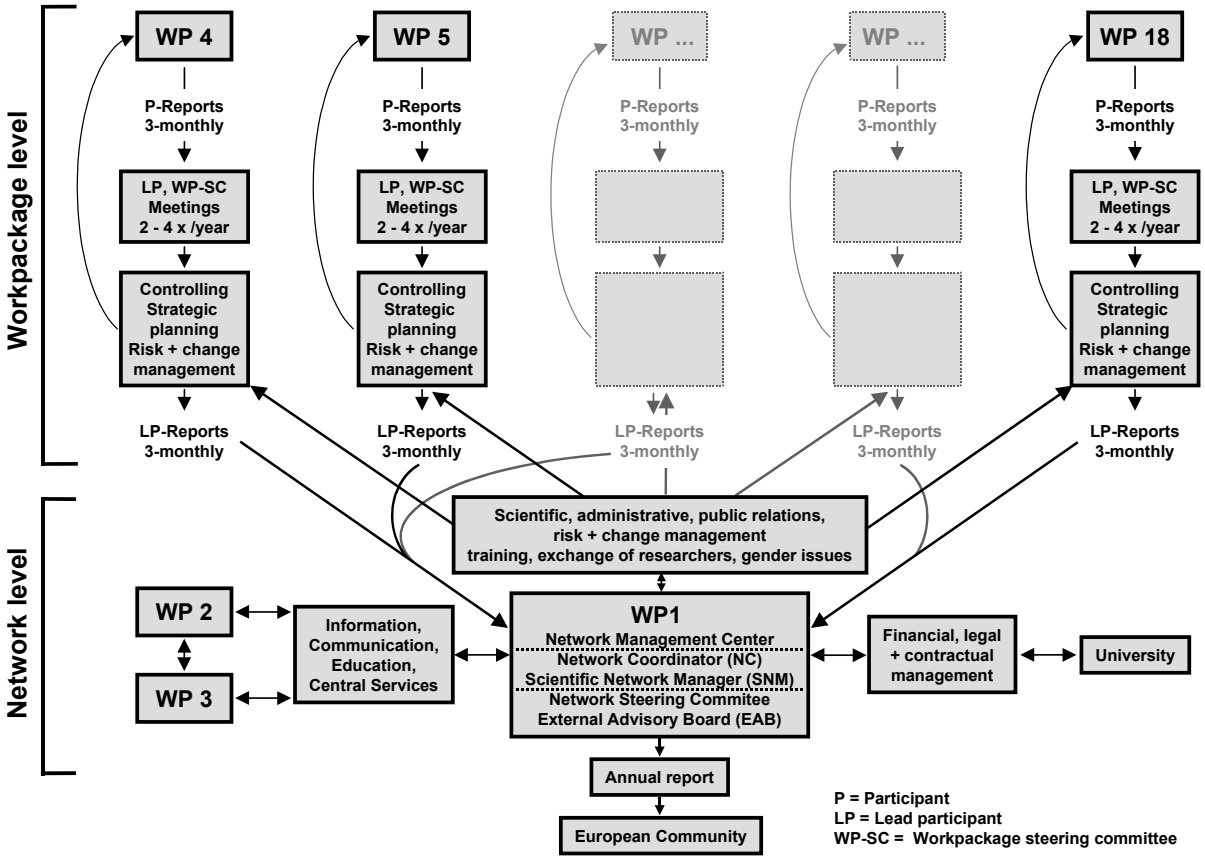

Fig. 10 : European Leukemia Net, management process and activities. For network organization see Fig. 11 (section 8.1). Network steering committee: Berger (Scientific Network Manager, WP 1), Gökbuget (WP 2), Müller (WP 3), Simonsson (WP 4), Burnett (WP 5), Hoelzer (WP 6), Hallek (WP 7), de Witte (WP 8), Barosi (WP 9), Béné (WP 10), Fonatsch (WP 11), Grimwade (WP 12), Haferlach (WP 13), Niederwieser (W 14), Ljungman (WP 15), Serve (WP 16), Hasford (WP 17), Gluckman (WP 18-Spread of excellence), O'Brien (WP18-Guidelines), Hehlmann (Network Coordinator)

Each WP-Participant will prepare 3-monthly progress reports (one page, standard format, bullet point style) on state of deliverables, milestones, compliance with time schedule or unexpected problems

interfering with the planned performance of research work. These reports will be discussed by the lead participant(s) and the steering group at their regular meetings at 3-6 month intervals.

The steering committee is responsible for controlling the performance of the WP activities and for strategic planning of the WP including risk and change management.

The risk and change management comprises all management activities that are required when deliverables relevant for the progress of research of the workpackage cannot be delivered or if other events occur that require new planning of research activities.

The lead participants are specifically responsible for ensuring that the implementation of their workpackage is consistent with the overall implementation plan and with the other network components. This entails in particular:

- The continuous monitoring and reporting of the implementation of the tasks within his/her workpackage,
- Keeping informed the SC and the SNM of progress made in his/her workpackage,
- Keeping the SC/SNM informed of any problems arising, and
- Ensuring that the interaction between his/her workpackage and other network workpackages and tasks are consistent with the specifications included in the detailed and overall implementation plan.

To this end, the lead participants will prepare quarterly summary reports for SNM and SC (1 page, same format as above) on their workpackage.

On the level of the clinical trials the quarterly reports should contain:
- Progress with clinical trials (number of trials, number of recruited patients, number of participating centers, etc.)
- Number and quality of drugs and treatment strategies involved,
- Extent to which uniform common data sets have been employed and used for standardizations of trial protocols and registration,
- Number of patients registered to the central registry.

Network level
The network is managed by the network coordinator (NC), the scientific network manager (SNM) and the network steering committee (SC) through the network management center (NMC, WP 1).
The network steering committee consists of all lead participants, the network coordinator and the scientific network manager. They will meet every three months, discuss the reports of all work packages and decide whether all activities can continue as planned or new avenues have to be used.
NC, SNM and SC are responsible for carrying out all scientific activities planned by the network and for preparing the annual report to the EC.
The SC is the central body for scientific controlling.

6.1.4.2 Technical and administrative management

The technical and administrative management concerning dissemination and knowledge management, quality and risk management and opportunity and change management will be carried out by the network management center (NMC, WP 1).

The NMC (WP 1) is the central body for **dissemination of knowledge** generated by the network. It collects information from the workpackages and provides the information with the help of CICS (WP 3) to the network information center (ELIC, WP 2). ELIC structures the information according to leukemia and user needs and includes the information in the internet website for intra- or internet use

according to user profile. In addition, newly generated knowledge will be disseminated by the regularly appearing newsletters (biannually), workshops, training courses and symposia which will be organized by NMC to foster spread of excellence.

The NMC will be advised by an **external advisory board (EAB)** which consists of representatives of science, medicine, culture, media, sports and politics. They will give advice regarding more general aspects such as public needs and acceptance of the network activities. They also can help with the multiplication of network impact and with public acceptance by European citizens.

Furthermore, the NMC will guarantee, that the sustainability of the network after community funding is not in danger. It is expected that all network activities will continue after the EC-funding period with funding from other sources or with institutional support since networking predictably will yield a higher efficiency of medical care at lower costs. The information extracted from the registries will be highly valuable for future planning of public health measures and allocation of public funds. In addition, it is expected that user organizations such as the EBMT will have an interest in the continued availability of registry data from the leukemia network.

Finally, the NMC will channel the information delivered from the network to the needs of patients and public health organizations and translate these requirements into a continued successful performance of networking.

6.1.4.3 Financial, legal and contractual management

The NMC will be supported by the expertise of the University of Heidelberg with regard to financial, legal and contractual management.

6.2 Plans

6.2.1 Plan for using and disseminating knowledge

Plans for management of knowledge and intellectual property
The intellectual property rights will be regulated among the contractual partners in the consortium agreement. This includes the pre-existing knowledge, including the connected rights, (copyrights, patent rights), the exclusion of pre-existing knowledge and the results and informations resulting from the project, including the connected rights. The principles of the FP 6 relating to possession rights, access rights and rules for exploitation find notice. The obligation to prosecute violation of intellectual property and of knowledge will be taken seriously particularly concerning rules for confidentialty. The management and comprehensive dissemination of network results and knowledge includes training and education activities, organization of symposia, workshops and conferences, participation in exhibitions, scientific publications, and permanent active public relation (PR) activities including the creation and maintenance of a network internet page, information to media, an events calendar and a newsletter.

Description of the use of the results
Most results of the network such as the creation of IST structure, trial platforms, standardization, registry and the like will not be patentable. Patentable results are only conceivable on special methodological territories. For patent capable research results, industrial partners will be found. Progress in diagnosis and therapy will be spread through publications and through reports on conferences and symposia as well as through the internet website of the network (NMC, ELIC, CICS, guidelines platform). It is expected that the results of clinical trials are not patentable either. But it is expected that the involved industry partners, whose products come to increased use through the study results, are appropriately involved in the costs of the network.

The network will overcome European fragmentation, will strengthen interdisciplinary information and communication among researchers, clinicians and scientists and ultimately improve patient care.
Distinct and different plans for exploitation and further investigation are existing in each workpackage.

The creation of **central information and communication structures** will provide the mechanism for spreading advanced and structured information to health care personnel, patients and their relatives, politicians and to the public at large. Networking will be supported by the Central Information and Communication Services with internet presence, homepage and trial support. Some results such as the set-up of a web-based registry of leukemia studies, a web-based patient recruitment and randomization facility, telemedicine with an exchange of image data for diagnostics and DNA profile determination, conferences, training courses, workshops, exchange of researchers, newsletters and print media will faciliate knowledge dissemination and spreading of excellence to health care personnel, researchers and to other countries not yet participating in the network. The rotation and exchange of young scientists might create new and unforeseeable career opportunities, will promote knowledge and technology transfer and enforce partnership in European research.

European networks for each leukemia with own homepages will contribute to standardization of diagnostic and therapeutic procedures and to metaanalyses and guidelines which will be published. They will participate in the organization of workshops, training courses and exchange of researchers.

The **European leukemia registry** will be based on the provision of common data sets collected in a uniform fashion. The registry will address a number of important research topics in the fields of epidemiology and risk factor analysis, predictors of survival and treatment response. This includes the determination of incidences and disease patterns across Europe including gender, age and ethnic differences as well as familial aggregations, overlap syndromes or precursor conditions. The benefits relate to large sample size collections, uniform data collection, an appropriate support by biostatistics and data processing and the connection with decentralized biobanks for prospective and retrospective studies with multiple research possibilities. Future investigations with the use of the collected data will identify patients with high risk profiles, correlate gene arrays to identified risks, define prognostic markers and develop new tumor models for pharmacological research on cancer. The longstanding experience in collecting data, performing metaanalyses and establishing prognostic scores guarantees qualified scientific output. This **data base** will have **far reaching implications for research and public health planning** far beyond the period of EC-funding.

European platforms for each interdisciplinary specialty will contribute to **standardization of diagnostic and therapeutic procedures, quality control of registries,** development and clinical testing of new drugs and recognition of new targets, performance of metaanalyses, development of clinical guidelines, workshops, training courses and exchange of researchers. The whole spectrum of rapid drug discovery and development of cancer therapies with an alliance among academia, industry, SMEs, government and patients will be the goal. The European Leukemia network will advance knowledge in all fields of leukemia and will play the pivotal role for standardizing diagnostic procedures (quality assurance), establishing standard data sets for clinical trials conducting intergroup trials and providing sufficient patient numbers to study rare subentities.

The conduction of clinical trials within **clinical trials platforms** for each leukemia **will improve patient care** and attract pharmaceutical industry looking for suitable clinical partners. Other results of interest will be **risk factor associations in the genomic era**, information on prognosis, **gene-environment interactions** or genetically defined leukemia subtypes and gender specific differences. The development of specific therapeutic trials for the various leukemias, the exchange of current trial protocols, the internet-based registry of ongoing trials will further promote and spread knowledge.

Standardization of diagnostics and therapy constitute the basis for good patient care, successful treatment and improvement in outcome. By successful, large clinical trials, metaanalyses of specific subaspects, the elaboration of prognostic scores, uniform data sets for study protocols, introduction of standards in molecular diagnostics, harmonization of transplant procedures, and the development of evidence based guidelines standardization of leukemia treatment will be promoted. The establishment of standards for the whole spectrum of diagnostic and therapeutic approaches in all fields of leukemia **will raise the quality of research and patient care and will be cost-effective**.

In detail, for morphological diagnosis ISDN-based telemicroscopy, interdisciplinary internet discussion rounds, quality control rounds as well as an European slide and multimedia bank are to be developed. Commercial use of the technical solutions may be possible, the contribution to spreading of kowledge is estimated to be higher.

The cytogenetics WP will provide new methods and develop software for analyses of large data sets which could be the basis for **commercial exploitation**.

The MRD section develops and standardizes molecular assays in the context of quality control, identifies new targets and fusion genes for MRD monitoring and implements the MRD assessment in the clinical setting with adequate timing schedules and standardized approaches to data analyses. The assays could be commercially used in cooperation with industrial partners.

The analysis of large gene expression data sets will identify new molecular targets for therapy. A software for gene profiling could be marketed. Consensus protocols for genetic techniques, standardized protocols and guidelines will be available and disseminated through expert forums and workshops.

The **harmonization** of indications for stem cell transplantations and the standardization of procedures with the determination of optimal protocols, promises to yield **cost relevant results with impact on the medical budgets throughout Europe**. In the fields of **supportive care** and anti-infection prophylaxis and therapy, new diagnostic assays, diagnostic procedures, techniques, monitoring protocols, and the antimicrobial prophylaxis and screening modalities will improve health care, probably at lower costs.

The perceptions within the European LeukemiaNet will not only lead to a better understanding of leukemias, but have important implications for treatment approaches to other tumors. The results of consensus and standardization protocols as well as harmonization, prophylaxis and screening modalities will be published in peer reviewed journals and will set European standards.

When randomized studies are available **metaanalyses** will be performed. On their bases evidence-based **guidelines,** consensus reports and expert reviews will be compiled and published by specialists from clinical trial groups and diagnostic platforms. It is the goal to publish guidelines for all leukemias and related syndromes within the project. They will be used to set standards for patient management and for educational purposes in training programmes and workshops.

Table 5: Use of the results of the network

Blocks of activities	Results	Use of the result
Central information and communication structures	Internet-presence, homepage, web-based registry, web-based randomization	The technical solutions may be commercially exploited, further investigations on user-friendliness and acceptance are implemented
	Telemedicine with data exchange for diagnostics and DNA-profiling, telemicroscopy, internet-discussion rounds	Improvement of the technical solutions in cooperation with industrial partners
European networks for each leukemia	Registries	Standardization, metaanalyses and guidelines for publication and quality control
Clinical trials platform	Multiple clinical trials with European protocol standards	Further research according to metaanalyses and final analyses, cooperation with industry for funding , publications, education
European leukemia registry		Publications in epidemiology, risk factor analyses, predictors of survival, outcome analyses
	Common data sets	Use for various studies and for public health planning
	Data bases for researchers	Unique source for clinical questions and investigations
	Decentralized biobanks	Prospective and retrospective studies
	New biostatistical methods, prognostic model analyses and metaanalyses	Further research, publications
Diagnostic, therapeutic and biometric platforms	Improvement of diagnostics, development and clinical testing of new drugs and targets with rapid drug discovery	Cooperation with industry, SMEs and government for commercial and clinical exploitation
	European diagnostic reference panel	Publications, education, training, quality control
Standardization		Large clinical trials, publications in various fields, cost effective screening, diagnostic and therapeutic modalities
	European slide and multimedia bank	Availability for the public and for experts, continuous improvement of the information
	Software to analyse large data sets	Further investigations i.e. for drug therapy, commercial exploitation of software solutions
	Molecular assays, genomic microarrays, software for assay/array data analyses	Cooperation with the industry for exploitation
	Gene profiling	Further investigations i.e. for drug therapy
	Techniques in handling antimicrobial infections	Cooperation with the industry by development and distribution, publication of findings
	Training courses, workshops, exchange and rotation of researchers	Quality control, indirect cost effectiveness
Metaanalyses and guidelines	Metaanalyses, guidelines, expert reviews, consensus reports	Publications for all leukemias and related syndromes, indirect cost effectiveness
	Production of software for guidelines on palm/pocket PC	Possible commercial exploitation in cooperation with SMEs

Plans for dissemination of knowledge beyond the consortium during the lifetime of the action and afterwards
The communication structure shall guarantee a prompt and adequate propagation of information and knowledge to the concerned groups within the network, to external partners and to the public at large. The NMC is the central body for dissemination of knowledge generated by the network. The lines to disseminate knowledge are as follows:

- Information is provided by the WPs at regular intervals to the NMC
- The SC/NC provides formal or official reports to ELIC
- ELIC provides structured informations to users and includes the information in the internet website for intra- or internet use according to user profile.
- Additionally there will be dissemination by workshops, training courses and symposia which will be organized by NMC to foster spread of excellence. New information will also be disseminated by the regularly appearing newsletters

Scopes for management of dissemination are:
- **Internet Homepage** – A homepage (www.leukemia-net.org) with distinct access levels including an Intranet for exchange of documents and data between the network partners as well as a public part, where news, network information and deliverables are available for the different target groups as far as they are approved by the EC will be posted once the project
- **Training and education activities** – will be organized and managed by the NMC in close collaboration with WPs 2-18.
- **Symposia of the Network** – at least once a year will raise the profile of the Consortium at a European and international level.
- **Public workshops** – Each workshop organizes public workshops twice a year to spread kowledge and to enhance public visibility.
- **Newsletters** will be implemented at six month intervals.

After community funding has ended it is expected that most network activities will continue. Thus the sustainability will be promoted by funding from other sources or with institutional support. It is expected that particularly the information from registries will enable future planning of public health measures and will be of high public interest. Standardizations will yield a higher efficiency of medical care at lower costs and thereby will have durable effects. In addition, user organizations such as the EBMT will not abstain from the continuous availability of data from the leukemia registries.

A comprehensive dissemination of network results and knowledge requires training and education activities, organization of symposia, workshops and conferences, participation on exhibitions, scientific publications, and a permanent active public relation (PR) activities including the creation and maintenance of a network internet page, information to media, an events calendar and a newsletter.

6.2.2 Gender Action Plan

The way, by which clinics and research are run in Europe, has traditionally been by and large a men's affair. Yet gender balance is achieved at the student, M.D. or Ph.D. in training or assistant professor level. In contrast, despite lacking representative statistics on women in decision-making positions in the field of hematology the general impression that women are severely underrepresented in strategic decision-making, planning or top research positions in most European countries appears well justified. The reasons are manifold but likely are rooted in deep seated cultural resistance against the evolving roles of gender per se in modern society.

The call is for all European institutions particularly those operating in the public sector to consider strategies for women to gain equal access to resources, security and enpowerment and to devise an agenda for action-oriented research.

Promotion of talented women researchers, resources of half of society yet obtaining 10% or less of top positions, would achieve better understanding, better health outcome and probably better response to the interests and concerns of the population as a whole. The European Leukemia Network is aware of its influence for a change of clinical practice by fostering new ideas and closer attention to everyday-life of people, both women and men. The Network's Steering Committee will ensure a policy of supporting the promotion of women scientists on each level within the subnetworks. This means that female students and scientists will be encouraged to take part in projects and that experts will take responsibility to support participation and integration of women.

As major tasks of their WPs the lead participants Dr. Ute Berger for NMC and Dr. Nicola Gökbuget for ELIC, will assume responsibility for integration of gender related issues and – research within the European Leukemia Network. In detail, ELIC will develop concepts how best to evaluate and promote gender equity in the European research area. NMC will more focus on specific gender issues within the European Leukemia Network. Dr. Berger and Dr. Gökbuget will act as network's Commissioners for gender policies. Their responsibilities will be as follows:

6.2.2.1 Survey situation of female physicians/researchers in the network

Only little is known about gender related problems in the field of hematology. Without this information it is however nearly impossible to define action plans for promotion of female researchers. One important aim of the ELIC (WP2) is therefore to generate electronic questionnaires to collect information on

- Characteristics of female scientists/physicians answering the questionnaire
- Professional perspectives, qualification and educational opportunities
- Employment and livelihood patterns, social and cultural practices
- Access to support services
- Support for female careers / for aspiration of leading positions
- Concepts for combination of family life and profession e.g. part-time work, day-care of children, return to professional life after maternity leave / children education

The questionnaire will be developed in cooperation with the organizations of female physicians in Germany. Results of these anonymous questionnaires will be provided to the Network Center and all network projects in order to adapt strategies for promotion of females if necessary.
Subsequently, follow-up surveys and reports will be delivered annually. These reports will suggest a wide range of positive action measures to achieve gender-balance:

- Identifying and transfer of pioneering models in Europe
- Collaboration with women support organizations
- Collaboration with other networks
- Spread gender specific information contents: besides discussion forum and funding opportunities etc. attention will be paid to leukemia specific topics.

The ELIC will also place a focus on gender-related information contents, which shall be provided on the website such as:

- Fertility preservation: Whereas widespread information about fertility preservation of male patients is available, far less is known about this issue for females. By specific information sheets on the website actual information on these questions will be provided for physicians and patients in cooperation with specialised gynecologists.
- Hormonal disturbances after chemotherapy: Information will be provided in order to increase awareness and improve therapeutic interventions.

- Leukemia in pregnancy: Although a rare condition all over Europe certainly a significant number of women develop leukemia in pregnancy. Experience with different types of leukemia, treatment schedules, time of pregnancy and outcome will be combined with general information on this issue.

6.2.2.2 Responsibilities of NMC for gender issues

The NMC will make special efforts to ensure that gender issues are addressed within the network and to strengthen strategies for reducing gender disparities. Various participating institutions, for instance the University of Heidelberg, to which the NMC belongs, already have detailed gender action plans in effect. As first step, alignment of existing gender action plans will be sought by the NMC with emphasis on

- Setting guidelines for promotion
- Considering special needs for women, at least compensate for adverse impacts on women
- Adapting training programs and revising educational curricula in a more gender conscious way
- Formulating a dissemination plan with directing attention of policy makers toward research specific gender issues

In close collaboration with ELIC, the NMC will coordinate the process of monitoring gender balance implementation within the network. Individual WPs and their lead participants will be responsible for implementing their own gender equity policy. Performance of gender issues will be incorporated into audit reports. The targets are set to achieve gender balance in the highest positions of strategic management and leadership.

6.2.2.3 Gender aspects in research

	Yes	No
Does the project involve human subjects?	●	
Does the project use human cells / tissues / other specimens?	●	
If human subjects are not involved or human materials not used, does the research involve animal subjects or animal tissues / cells / other specimens *(as models of human biology/physiology)* in such a way that it is expected that may have implications for humans?	N.A.	
Does the project use collection of data related to human subjects, human materials, animal subjects or animal materials	●	

	Yes	No
Are gender/sex differences with respect to the research documented in the literature?	●	

Participation of women in the project

Are there women directly involved:

- in the scientific management of the project? Yes [x] No
- in the scientific partnership as scientific team leader in the project? Yes [x] No

- % of women scientists involved in the project:

➔ Lead Participants 17 %
➔ Associated Scientists 22 %
➔ Experienced researchers (minimum 4 years after graduate or having a PhD) 40 %
➔ Early researchers (less than 4 years after graduate) 57 %

Overall 36%

- One third of the WPs (6 out of 18) have a female lead participant. Women are also represented as associated scientists in all WPs. WP 2 predominantly involves female scientists.
- If additional staff for the project is required, the following procedure is used at universities in Germany and is suggested for use in other European countries. Advertisements for all new employees contain the following passage: „Females are explicitly encouraged to apply for this employment. In case of equal qualification, females are preferentially employed".
- This procedure has been proven successful in the past.
- In advertisements women who return to professional life after children education will be explicitly encouraged for application.
- Furthermore, for all new jobs within the project the possibility of part time employment and flexible working hours will be offered. This is highly compatible with the necessary work. Also online work from home could be considered in special cases.

Gender research focus within the European Leukemia Network.
Only little is known about gender related problems in the field of hematology. Most information relates to the longevity of women as compared to men. Leukemias that have their incidence maximum in older age tend to have female predominance. In CML the male to female ratio overall is 60:40%. In patients older than 60 years the ratio is reverse, being even more pronounced in higher age groups. Male CML-patients have significantly larger spleen sizes which, however, have no impact on survival.

The incidence of ALL similarly shows a male preponderance. Whereas in childhood ALL (<10 years), the incidences within males and females are nearly equal, there is male preponderance up to 3:1 in adolescence and adults and an equal distribution in patients older than 80 years. The difference in adult age is mainly related to the steeper increase of incidence in males than in females. In addition, there are even greater differences of gender specific incidences in subtypes of ALL, e.g. a high male preponderance in T-ALL. These differences can only be concluded from study groups, but not from epidemiological registries, since details of subtypes are not available in registries. A variety of potential factors have been sporadically reported and could be associated with gender specific differences and incidences of all leukemias such as occupation (e.g., reported excess mortality of female hairdressers from non-Hodgkin's lymphoma and lymphoid leukemia), infectious agents, hormonal influences, genes on Y or X chromosomes, chromosomal aberrations (female predominance of trisomy 8) HLA system (e.g., gender differential disparities of minor histocompatibility antigens), psychosocial factors (e.g., coping techniques), pharmacokinetics of cytostatic drugs, availability of stem cell donors.

Most of these questions are not addressed in clinical studies and none has been demonstrated to be relevant so far. Therefore an important goal of the leukemia network will be to combine available information on gender specific differences and to consider these issues for specific risk projects. Correspondingly all leukemia WPs will address gender specific issues as special objectives.

Outcome research
Literature data are showing that for children with ALL the outcome is influenced by gender. Boys have a poorer outcome than girls. Reasons for that difference are in part the poorer outcome of boys with testicular involvement, the higher testicular relapse rate but also the higher rate of bone marrow relapses which may arise from minimal residual disease in testis. This may be translated to gender specific treatment approaches such as prolonged maintenance therapy in males, intensified use of high-dose methotrexate etc.
It is so far unknown whether there is a difference in the cure rates with respect to gender for adolescents (a very important age group), adult or elderly ALL patients. Enforced by this research program, a reanalysis of a large cohort of adult ALL patients was started in 2002. Unexpectedly, in this cohort the outcome for female adolescent and elderly ALL patients was inferior. These results have to be confirmed or extended to a large data set as available in the European Leukemia Network.

An attempt has to be made to investigate the underlying mechanisms and circumstances, e.g.

- biological and prognostic markers
- treatment feasibility and compliance
- availability of stem cell donors
- and hopefully arrive at effective prevention measures and *devise gender specific guidelines*.

Also transplantation outcome is influenced by gender issues since the combination female donor male recipient has the poorest outcome. This is attributed to the sensitization of the HLA system by previous pregnancies, probably also by blood transfusions.

Long-term side effects and survivorship research

Little is known about the late effects of therapy of adult ALL and in particular on gender related differences. This may include for instance fertility, bone density, hormonal disturbances, incidence of secondary malignancies, or quality of life. The network will aim to increase the awareness of these issues and to support projects in the field.

Gender-specific differences can be identified for various issues in all leukemias, but little research on causes and potential consequences has been performed. The network will therefore aim to perform joint analyses of gender-specific differences of

- Biological and clinical markers
- Treatment outcome
- Long term effects

6.2.3 Raising public participation and awareness

New communication media facilitate the access to state-of-the-art leukemia treatments for patients and the public. General information, medical decision-making and questions of quality of life of cancer patients are important. Patients suffering from leukemias are especially dependent on effective information. Therefore the Internet homepage – the homepage of the European LeukemiaNet (www.leukemia-net.org) will be installed once the project starts and will be used as a important communication and information platform for experts and the public. Advertising efforts have to be made to augment the perception of the network as a whole and the homepage in particular.

Since the participating groups represent the major opinion leaders in their countries the set-up of the European LeukemiaNet will contribute to public health in their respective countries. By the promotion of knowledge on new treatment approaches created in the network and subnetworks rapid transfer into clinical practice is expected. In addition the European LeukemiaNet is ambitious to disseminate state-of-the-art therapy into community practice, publish findings in scientific journals and conferences, thereby enhancing public awareness. When standards for treatment approaches, methodology and leukemia diagnostics are published in major peer reviewed journals this will reach influential health related organizations of society such as insurance companies, health policy makers, medical societies, universities, teaching and training institutions. The initiation of education programmes and curricula on a European level will follow.

To raise public awareness the many different groups in society that may use the network results for their own work including teachers, industry, health insurance companies, politicians, sponsors, cancer organizations, or the interested public shall be involved and asked for contribution. In addition, representative key stake holders, i. e., patient or professional organizations, politicians, artists are already or will be invited to participate. The German network is proud to have won Mr. Jose Carreras and Mr. R. Völler, coach of the German national football team for public relations promotion.

The resources available in the Comission for media and information activities will be used and a participation in the annual European Science Week is planned.

PR activities, resident at the NMC and fostered by a public relations specialist are contributing at public events such as press conferences, stands at national and international meetings and conferences, TV and radio appearances. Press kits, patient information material, flyers, brochures and newspaper articles are being developed and distributed.

Finally, a newsletter will be implemented at six months intervals.

6.3 Milestones

6.3.1 Major milestones over full duration of the action

The major milestones of the single work packages are part of the joint programme of activities which are described in more detail for the first 18 months in section 9.

Milestones full period	Timing Month 1 – 60
NMC (WP 1)	
Set up of the administrative infrastructure, action plan	1 – 6
Project presentation	6
Organization of internal and external reporting ensuring that milestones are effectively reached	4x / year
Organization of regular meetings held by the Steering Committee	4x / year
Organization of Annual Network's Symposium	1x / year
Integration of clinical trial networks and interdisciplinary platforms, progress report	1x / year
Deliver all integrated trials to the integrated web site, progress report	1x / year
Annual reports to EC	1x / year
Issue of the biannual network's information letter in conjunction with ELIC	2x / year
Meeting to set up criteria for accreditation of trials	18
Accreditation of new clinical trials	19 – 60
Integrating new partners, industry and key stakeholders including patient organization, support activities that constitute synergism, e.g., cooperations, partnership, funds	19 – 60
Operating rotation and exchange programs for scientists and trainees	19 – 60
Final evaluation of the network's structure and impact, proof that it works	57 – 60
Institutionalisation of the European LeukemiaNet	60 – 72
ELIC (WP 2)	
Set up of WP management structure with lead participant and WP steering committee	1 – 6
Set up homepage template with overall structure – sustain and expand	1
1st e-mail information letter (3-monthly)	4x / year
1st Questionnaire on information needs and priorities	6
Full operating website template with access levels and registration	6
Issue of the biannual network's information letter in conjunction with NMC	2x / year
Concept and first contents study registry	8
Concept and first contents laboratory registry	10
Integrate basic information on all projects	12
First Contents for Patient information on different leukemias	15
Survey with online questionnaires for evaluation of website	18

User analysis and quality control	24,36,48,60
Major contents of study data base	24
Patient information for leukemia subtypes in major European languages	36
Institutionalisation of ELIC and concept for maintenance	48
Website certification	60
Final evaluation of ELIC‘s structure and impact	57 – 60

CICS (WP 3)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on WP available	6
Development and operation of central web-based patient recruitment and randomization facility	3 – 18
Development and operation of central electronic data capture facility	6 – 18
Continued operation of central IT and patient recruitment	19 – 60
Continued operation of central electronic data capture for clinical trials	19 – 60
Final evaluation of the network’s IT-structures and their impact	57 – 60

CML (WP 4)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on CML available (information on structure and trial activity of national CML trial groups, exchange of study protocols of open clinical trials)	6
Creation of WP management structure with lead participant and WP steering committee	6
Integration of European CML platform, EICML – web site	6
Utilization of common uniform data sets for newly activated clinical trials	6 – 60
Formation of a subcommittee for the registry of CML trial patients	12
Definition of rules for a European CML registry and of subprojects	12
Establishment of the protocol for a European CML registry	12
First proposal of definitions and standardization of relevant diagnostic and therapeutic procedures	12
Network structure functioning to define and standardize future diagnostic and therapeutic procedures	19 – 60
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Set up criteria for accreditation of trials, start date	19 – 24
Accreditation of new clinical trials	25 – 60
Final evaluation of number of clinical trials initiated and completed	54 – 60
Continued operation of European CML network	19 – 60
Final evaluation of the WP’s structure and impact	57 – 60

AML (WP 5)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on AML available	6
Creation of WP management structure with lead participant and WP steering committee	6
Creation of European AML platform	6
Agreement of leading European trial groups to join the network	6
Common uniform data sets available	12

First proposal of definitions and standardization of relevant diagnostic and therapeutic procedures	12
Integration of several new trial groups on the basis of international common protocol standards	12
European consensus on principals and instruments of cross trial networking, start date	18
Network structure functioning to define and standardize future diagnostic and therapeutic procedures	19 – 60
Set up European AML registry from trial patients	19 – 24
Spreading of excellence by promotion of web-based information, exchange of researchers, education/training courses, calendar, slides and promotion of guidelines	19 – 60
European AML networking protocol and amendments to trial protocols	19 – 60
Implementation of networking instruments such as general upfront randomization and common standard arm	19 – 60
Cross trial networking using general upfront randomization and common standard arm	19 – 60
Set up criteria for accreditation of trials, start date	19 – 24
Accreditation of new clinical trials	25 – 60
Network structure and trial platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

ALL (WP 6)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on ALL available	6
Creation of WP management structure with lead participant and WP steering committee	6
Creation of European ALL platform	6
1st Workshop during European meeting	6
Activation of first European intergroup study	12
First proposal of standards for relevant diagnostic procedures	12
Concept for an European ALL registry on rare subgroups (definition of uniform data set)	18
Concept for 1st joint analysis	18
Network structure functioning to define and standardize future diagnostic and therapeutic procedures	19 – 60
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Inclusion of additional partners in network	19 – 60
Accreditation of new clinical trials	19 – 60
Network structure and trial platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

CLL (WP 7)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on CLL available	6
Creation of WP management structure with lead participant and WP steering committee	6
Creation of European CLL platform	6
Exchange of study protocols of open clinical trials, information on structure and trial activity of national CLL trial groups	12
First proposal of definitions and standardization of relevant diagnostic and therapeutic procedures	24
Network structure functioning to define and standardize future diagnostic and therapeutic procedures	25 – 60

Prepare clinical practice guidelines with emphasis on the indications for chemotherapy with purine analogues, as well as auto- and allografting CLL – starting date	19
Define indications for stem cell transplantation in CLL	19
Proposal on harmonization of CLL transplant protocols and procedures	19
Common uniform data sets available	25
Set up European CLL registry	25
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Set up criteria for accreditation of trials, start date	25 – 30
Accreditation of new clinical trials	31 – 60
Network structure and trial platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

MDS (WP 8)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on MDS available	6
Creation of WP management structure with lead participant and WP steering committee	6
Creation of European MDS platform with integration of several new trials	18
Formation of a subcommittee for the registry of MDS trial patients	12
Definition of rules for a European MDS registry	12
Establishment of the program for a European MDS registry	12
First proposal of definitions and standardization of relevant diagnostic and therapeutic procedures	12
First draft of agreement of leading European MDS trial groups to join the network	12
First proposal of European consensus on the guidelines for diagnostic standards	12
Common uniform data sets available	18
Cytogenetic abnormalities as prognostic factor in MDS, first evaluation	19 – 30
Implementation of networking instruments such as general upfront randomization and common standard arm	19 – 30
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Network structure functioning to define and standardize future diagnostic and therapeutic procedures	19 – 60
Phase I/II trials (5-azacytidine, thalidomide, farnesyltransferase inhibitors, arsenic trioxide and others)	19 – 60
First positive interim analysis of network-wide prognostic model guided treatment strategies	36 – 60
Set up criteria for accreditation of trials, start date	19 – 24
Accreditation of new clinical trials	25 – 60
Network structure and trial platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

CMPD (WP 9)

Establishment of WP information and communication structures	6
Web-based information- and communication services on CMPD available	6
Creation of WP management structure with lead participant and WP steering committee	6
Creation of European CMPD platform	6
First proposal of diagnostic, prognostic and staging definitions of CMPD to be used in clinical trials	12

Registry of clinical trials in CMPD	6
Registry of CMPD variant forms, subtypes and rare complications	12
Proposal on harmonization of CMPD transplant protocols and procedures	18
Common uniform data sets available	24
Utilization of common data sets for newly activated clinical trials	25 – 60
Network structure functioning to define and standardize future diagnostic and therapeutic procedures	19 – 60
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Set up criteria for accreditation of trials, start date	19 – 24
Set up European CMPD registry	30
Accreditation of new clinical trials	25 – 60
Network structure and trial platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

Diagnostic platform (WP 10)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on WP available	6
Creation of WP management structure with lead participant and WP steering committee	6
Creation of European platform for leukemia diagnostics	6
Internet forum for interdisciplinary discussion of challenging cases	12 – 60
Completion of the first European quality control round on (morphological) leukemia diagnostics on the „reference center level“,	12
Create a European diagnostic reference panel	12
Establish training courses on leukemia diagnostics on the European level	18 – 60
Establish regular consensus conferences on leukemia diagnostics on the European level	18 – 60
Establishment of common data sets for leukemia diagnostics	25 – 36
Set up European registry for leukemia diagnostics	30 – 36
Standardization of diagnostic procedures achieved	36
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Network structure and diagnostic platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

Cytogenetics (WP 11)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on WP available	6
Creation of WP management structure with lead participant and WP steering committee	6
Creation of European platform for leukemia cytogenetics	6
Set up a platform for forum to present difficult cases, ask for and provide additional methods for further investigations	12
Formation of a subcommittee for the registry of leukemia cytogenetics	18
Definition of rules for a European registry for leukemia cytogenetics	18
Establishment of the program for a European registry for leukemia cytogenetics	18
Establishment of a platform for data exchange with other subgroups of the network	12 – 18
Develop consensus protocols for each genetic technique adapted to the different diseases	19 – 60
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60

Develop agreed rules for developing a pan-network of cytogenetic data with clinical outcome	24 – 60
Standardization of cytogenetic procedures achieved	36
Network structure and cytogenetic platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

MRD (WP 12)

Establishment of WP information and communication structures	1 – 6
Web-based information- and communication services on WP available	6
Creation of WP management structure with lead participant and WP steering committee	1 – 6
Creation of European MRD platform	1 – 6
Design and optimization of RQ-PCR assays for rarer fusion gene transcripts and for novel over-expressed genes in leukemia	15
Establish the additional proportion of leukemic patients that can be monitored using novel targets	15
Development of optimized, sensitive validated assays for MRD detection	15
Development of standardized protocols for MRD assessment using RNA-based targets (from bedside to clinical report)	15
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Evaluation of validated RQ-PCR assays in National clinical trials	15 – 60
Analysis of gender specific issues	19 – 60
Network structure and MRD platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

Gene profiling (WP 13)

Establishment of WP information and communication structures	6
Web-based information- and communication services on WP available	6
Creation of WP management structure with lead participant and WP steering committee	6
Set up European gene profiling platform	6
First proposal to identify and group leukemia entities	12
First proposal to standardize platform and exchange data, personnel	12
First evaluation of new biostatistical methods	12
Detect new subgroups of leukemia according to gene expression profiles	18 – 60
Linking data to study groups and pharmaceutical industry for drug development to find new products for the treatment of leukemia	18 – 60
New targets for diagnosis and therapy identified	19 – 60
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Recognition of role for gene profiling in leukemia promoted	19 – 60
Analysis of gender specific issues	19 – 60
Network structure and gene profiling platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

Stem cell transplantation (WP 14)

Establishment of WP information and communication structures	6
Web-based information- and communication services on SCT available	6 – 18
Creation of WP management structure with lead participant and WP steering committee	6

Creation of European SCT platform	6
Kick off meeting for coordination and time table for educational meetings	2
First proposal of definitions and standardization of relevant diagnostic and therapeutic procedures	12
Common uniform data sets available	18
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Set up criteria for accreditation of trials, start date	19 – 24
Accreditation of new clinical trials	25 – 60
Standardized procedures of SCT by performing prospective studies and giving guidelines across Europe achieved	48 – 60
Epidemiologic evaluation of performed SCT under way	19 – 60
Epidemiologic evaluation of performed SCT completed	60
Network structure and SCT platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

Supportive care/anti-infection prophylaxis and treatment (WP 15)

Establishment of WP information and communication structures	6
Web-based information- and communication services on SCT available	6
Creation of WP management structure with lead participant and WP steering committee	6
Set up European anti-infective platform to initiate European multicenter studies using standardized criteria for initiation and response evaluation	12
Review and summarize existing protocols for galactomannan, qPCR and HR-CT scans to screen for IFI/monitor antifungal therapy	12
Plan and develop a platform for multicenter studies for infectious disease management in patients with leukemia	15
Collect and compare national guidelines for prophylaxis and treatment of infections in leukemic patients	18
Review and summarize existing protocols for monitoring of pathogen-specific immune response	18
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Collect and compare national guidelines for oropharyngeal infection in leukemic patients	19 – 24
Common standards and guidelines on current anti-infection procedures across Europe established	36 – 48
Platform for definitions and standardization of future approaches in operation	19 – 60
Analysis of gender specific issues	19 – 60
Initiate prospective European multicenter studies based on a standardized monitoring protocol of pathogen-specific immune responses	24
Network structure and anti-infective platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60
Final evaluation of the WP's structure and impact	57 – 60

Treatment research (WP 16)

Establishment of WP information and communication structures	6
First web-based information- and communication services on WP available, e.g. homepage "Drugs against Leukemia"	6
Creation of WP management structure with lead participant and WP steering committee	6
Creation of European platform for drug development/new targets	6

First proposal of definitions and standardization of relevant therapeutic procedures (phase I/II)	12
"Current Drug Target" repository	12
"Current Leukemia Models" repository	12
"Current Compounds" repository	12
"Current Drug Target" repository completed and regularly updated	19 – 60
"Current Leukemia Models" repository completed and regularly updated	19 – 60
"Current Compounds" repository completed and regularly updated	19 – 60
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Analysis of gender specific issues	19 – 60
Evaluation of compounds in pipeline	19 – 60
Joint performance of early clinical trials (jointly with clinical trial platforms)	24 – 60
Performance of associated laboratory research programs	19 – 60
Platform for the development of new drugs in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

Biometry of Registries, Epidemiology, Metaanalyses and Prognosis (WP 17)

Establishment of WP information and communication structures	6
Web-based information- and communication services on WP available	6
Creation of WP management structure with lead participant and WP steering committee	6
Integration into European platform	6
CML core data set finalized	6
Definition of rules for a European CML registry	12
Establishment of the program for a European CML registry	12
AML core data set finalized	12
Collect data for prognostic model analyses and meta-analyses	18
Spreading of excellence by promotion of web-based information, exchange of researchers, education/training courses, calendar, slides and promotion of guidelines	19 – 60
Analysis of gender specific issues	19 – 60
Definition of rules for a European AML registry	24
Definition of rules for other registries	36
Final prognostic models developed and validated	42 – 48
Implementation of validated prognostic models in guidelines	48 – 60
MDS core data set finalized	36 – 48
Network structure and registry platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

Guidelines (WP 18)

Establishment of WP information and communication structures	6
Creation of WP management structure with lead participant and WP steering committee	6
Gather current guidelines from around EU Central web resource	9
Use CML as a model for first guideline production on web	12
Production of CML guideline for Palm Pilot and/or Pocket PC	18
Spreading of excellence by promotion of web-based information, exchange of researchers, training courses and promotion of guidelines	19 – 60
Analysis of gender specific issues	19 – 60
Delivery of AML guideline on the web	24

Production of AML guideline for Palm Pilot and/or Pocket PC	24
Engage participation of 90% of EU countries in contribution and/or usage	24
Delivery of 2 'technology' guidelines based on the most appropriate from WP 10-15 on the web	30
Guidelines for all leukemias available	60
Network structure and guideline platform in operation	19 – 60
Final evaluation of the WP's structure and impact	57 – 60

7. QUALITY OF INTEGRATION AND PERFORMANCE INDICATORS

The joined program of activities cannot be achieved without the high degree of integration as described in section 6. In order to perform the major 8 blocks of activities all clinical trial and expert groups in WPs 1-18 have to cooperate within a two layer integration:

- Within each WP across Europe and
- Within each block of activities according to objectives and activities.

All participants have made a commitment towards a deep and durable integration as documented by the 117 letters of commitment from the executive bodies of their organizations listed in this section and included in the annex.

The quality of integration will be profoundly influenced by the quality of information and communication within each workpackage and within the network. The immediate installation of an IT infrastructure by CICS and the provision of structured information by ELIC for all workpackages, network participants, scientists and the network at large will provide a meta-information system of high quality and impact.

The integration is comprehensive regarding

- Integration of trials
- Interdisciplinary integration
- European integration
- Instruments of integration (IT structure, training, workshops, information)

The quality of European integration within this network is illustrated (table 6) by the integration of eight ALL trial groups from seven countries and one European organization within one workpackage (WP 6, ALL).

Table 6: Integration of eight ALL trial groups from seven countries and one European organization within one workpackage

Abbreviation	Group	Workpackage Scientists
EORTC **European**	European Organizsation on Treatment and Research in Cancer, Leukemia Working Group	Prof. B. Labar Prof. R. Willemze
GRAALL **France Switzerland**	Group for Research in Adult ALL (including cooperative groups in France and Switzerland) GOELAMS : Groupe Ouest Est des Leucémies Aiguës et Maladies du Sang SAKK: Schweizer Arbeitsgemeinschaft für klinische Krebsforschung	Prof. H.Dombret Prof. N.Ifrah Dr. T. Kovacsovics
GIMEMA **Italy**	Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto	Prof. F. Mandelli Prof. G. Meloni Prof. R. Foa Dr. L. Annino
GMALL **Germany**	German Multicenter Study Group for Adult ALL	Dr. N. Gökbuget Prof. D. Hoelzer
NILG **Italy**	Northern Italy Leukemia Group	Dr. R. Bassan
PETHEMA **Spain**	Program for Study and Treatment of Malignant Hemopathies, Spanish Society of Hematology	Dr. J. M. Ribera
PLRG **Poland**	Polish Lymphoma Research Group	Dr. J. Walewski
HOVON **Netherlands**	Stichting Haemato-Oncologie voor Volwassenen Nederland (Dutch haemato-oncology association)	Dr. A. Dekker

Another example are the diagnostic workpackages and their integration with the clinical trial groups which are an integrating activity by themselves.

Integration will be fostered also in the future by an **open network structure**:
If an Integrated Project (IP) or Network of Excellence (NoE) application for MRD detection as a topic for the second call succeeds, WP 12 of this network (MRD detection) will be integrated in the planned IP or NoE to create a network-overlapping platform.
Integration of other groups addressing targeted therapy of cancers within other NoEs or IPs will be welcome at any time.

Four pieces of evidence argue for the **durability and sustainability** of the network beyond the period of community support:

- Most if not all standardizations will be of durable relevance
- The establishment of registries will provide data sets that will be available also after community support has been terminated
- Networking will be cost effective. The common use of information and communication services and widely overlapping objectives for all leukemias such as clinical trials, standardization, registry, clinical research, metaanalyses and guidelines facilitate a highly economical approach for all network participants. It is expected that all network activities will continue with funding from other sources since networking predictably will yield a **higher efficiency of medical care at lower costs**.
- The information extracted from the registries will be highly valuable for future planning of public health measures and allocation of public funds.

Finally, the personal cooperation within the NoE will have a lasting effect on personal relations and on the intimate knowledge of the cooperating partners, their institutions and their countries, creating a sound basis for continued collaboration and integration also in the future.

The following **performance indicators** will be used:

1. Quality of European integration
2. Accuracy of financial reporting
3. Accuracy and punctuality of progress reports
4. Develop sustainability of the network
5. Number and quality of administrative, strategic and scientific meetings held per year
6. Spread of excellence via educational activities
7. Number of new collaborations established
8. Number of rotating researchers in exchange programs (integration of manpower)
9. Implementation of quality control rounds or central diagnostic review
10. Spread of excellence via website
11. Quality of web-based information on clinical trials
12. Number of registered homepage users
13. Number of hits, visits at or downloads from the homepage
14. Number and quality of evaluation questionnaires, relevance of results
15. Quality of web-based information for lay persons
16. Number of clinical trials receiving biostatistical support
17. Number of clinical trials started and/or completed
18. Number of patients recruited or randomized into clinical trials
19. Number of patients included into registries
20. Number of patient data collected for prognostic factor analyses and meta analyses
21. Improved predictive-, prognostic- , or quality of life assessments
22. Degree of harmonization of trials methodology
23. Degree of harmonization of transplantation procedures
24. Number and quality of publications through joint research activities
25. Number of metaanalyses, consensus reports, or expert reviews in the field
26. Development and implementation of guidelines
27. Number of difficult cases presented in expert forums
28. Implementation of a continuous exchange of materials and knowledge
29. Implementation of technology transfer
30. Improved techniques with better results in diagnostics or therapy prediction
31. Number of standardized or validated diagnostic methods
32. Number of developped and validated prognostic models
33. Number of new leukemia subtypes identified
34. Number of new recurrent cytogenetic abnormalities identified
35. Number of disease-specific aberrations identified
36. Number of cytogenetic or molecular abnormalities for which the predictive or prognostic impact could be clarified
37. Number of gene expression samples for which the diagnostic, predictive or prognostic impact could be clarified
38. Number of disease-specific genetic markers and gene profiles identified
39. Number of identified potential therapeutic targets
40. Number of tested biological-relevant substances
41. Number of novel specific drugs transferred into clinical trials
42. Number of accredited trials

8. PROJECT ORGANISATION, MANAGEMENT AND GOVERNANCE STRUCTURE

8.1 European LeukemiaNet: network organization

The network organization diagram in Fig. 11 shows the detailed structure of the consortium organization. Different organizational units will work together for this network and are integrated on an equal level. The Sub-Networks consist of Work Packages (WP). The WPs are integrated in blocks of activities and single activity components for networking.

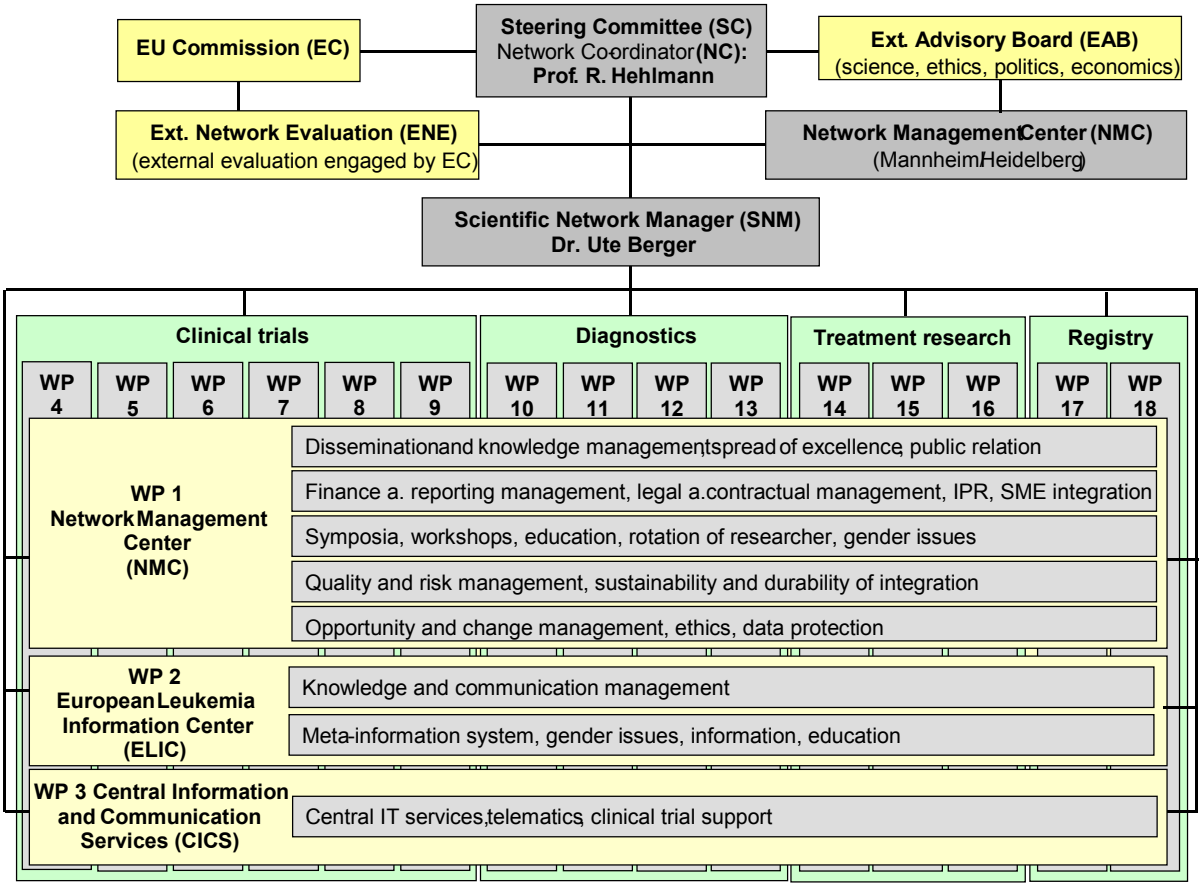

Fig. 11: Network organization diagram. Network steering committee: Berger (Scientific Network Manager, WP 1), Gökbuget (WP 2), Müller (WP 3), Simonsson (WP 4), Burnett (WP 5), Hoelzer (WP 6), Hallek (WP 7), de Witte (WP 8), Barosi (WP 9), Béné (WP 10), Fonatsch (WP 11), Grimwade (WP 12), Haferlach (WP 13), Niederwieser (WP 14), Ljungman (WP 15), Serve (WP 16), Hasford (WP 17), Gluckman (WP 18-Spread of excellence), O'Brien (WP18-Guidelines), Hehlmann (Network Coordinator) WP1: NMC, WP2: ELIC, WP3: CICS, WP4: CML, WP5: AML, WP6: ALL, WP7: CLL, WP8: MDS, WP9: CMPD, WP10: Diagnostics, WP11: Cytogenetics, WP12: MRD, WP13: Gene Profiling, WP14: SCT, WP15: Supportive care, WP16: Treatment research, WP17: Registry and Biometry, WP18: Guidelines For WP description and lead participant see list in 9.4. Participants' short names are provided in 3.1 (institutions) and 3.2 (scientists). Links between clusters and WPs are indicated in Fig. 16. The management disciplines are further detailed in Fig.12.

Each workpackage has its own role, competence, responsibilities and tasks in the network organization:

Network Governing Board
The Network Governing Board consists of one representative of all participants (Parties), the Network Coordinator and the Scientific Network Manager (SNM). These representatives are of senior executive management level and be authorised to decide on all matters necessary to carry out this Network. The decisions of the Network Governing Board in the Network-related matters are shall be legally binding to all participants subject to the right of each participant to veto any decision which essentially affects legitimate interests of them.

The Network Governing Board shall consider the report of the Network Co-ordination Committee, receive and approve the accounts for the past (financial) year, approve the budget and Annual Plan for Activities and acceptance of new parties or withdrawals or exclusion of Parties and decides on matters relating to:

- the preparation and final approval of the Annual Plan of Activities in accordance with the Joint Programme of Activities prior to the submission to the Commission,
- all budget-related matters,
- the acceptance of new parties as well as the exclusion of Parties,
- the structure and restructuring of the Network and Workpackages,
- legal guidelines for co-operation agreements (on a bi- or multilateral basis between the Parties), and
- proposals to amend the Consortium Agreement.

Steering Committee (SC) / Network Coordination Committee
The Steering Committee (SC) consists of the coordinating lead participants (LP) of the 18 workpackages, the network coordinator (NC) and the Scientific Network Manager (SNM). The scientific officer of the EU Commission (EC) will always be invited to the meetings of the Steering Committee.

The SC is in charge of the whole project and has the overall responsibility (for e.g. finances and sign-offs of deliverables). Decisions are made by consensus, and if not reached, by majority vote. The SC plans, manages and controls the European LeukemiaNet on a general level. It defines research goals and approaches and ascertains the progress of their realization, e.g. periodic review of progress. The SC acts as both sponsor and promoter at management level, duly supporting the network tasks and their successful completion. It decides on priorities, work plan corrections, problem resolution, calls for new partners or sub-contracts.

Network Coordinator (NC)
The Network is represented by the Network Coordinator, who also serves as the Chairman of the Steering Committee. The NC bears the overall responsibility for the smooth and prompt development of the project. In particular, the NC will continuously monitor the progress of the project and ensure that milestones are effectively reached, and that the criteria for their evaluation are met. The NC is responsible for reporting and communication to the EC, as well as for marketing of the project on an European level. The NC and the Scientific Network Manager (SNM) are the main contact persons for all matters outside the network.

External Advisory Board (EAB)
The External Advisory Board consists of a group of 5 to 10 experts from medicine, science, culture, media, sports, patient and vacancy groups and politics on a European level. The EAB will advise the SC in matters of science, ethics, politics or economics. It provides an independent external view on the project subjects and deliverables.

External Network Evaluation (ENE)
The EU Commission (EC) will conduct audits or entitle external project evaluators to do so. In particular, technical, financial, technological (innovation impact), and ethical audits for the European

Leukemia Network could be opportune. Various audits may be undertaken simultaneously. The diagram for reporting, payments and review schedule (see below) indicates five parallel technical and financial audits during the network life time.

External Network Controlling / Coaching (ENC)
The Network Controlling provides an external, independent view of network risks related to the achievement of the objectives (i.e. time, scope, cost and quality). Scheduling of risk assessments depends on the network status within the innovation life-cycle. The ENC introduces professional network management know-how into the network and supports NC/SNM/NMC when necessary (e.g. during a prompt and timely network set-up). The ENC will be set up by the NMC prior to activation of the network.

Scientific Network Manager (SNM)
The SNM ensures that the network is carried out as per network plan (time, cost, scope and quality). Her area of responsibilities includes all planning, steering and controlling activities, problem solution activities and corresponding administrative work. She is the contact point for both, superior and subordinate, units. Thus, the SNM is in the center of communication inside the network. Together with the NC she ensures a positive and motivational atmosphere for all network partners. The SNM is employed at the entity of the NC.

Network Management Center (NMC, WP 1)
The Network Management Center (NMC) supports the SNM in carrying out the overall network management on the administrative level.

Lead participants (LP) (s. list in 9.4)
Lead participants are appointed for each WP. As part of the overall activity plan the LP develop detailed realization plans for the respective WPs of their groups. For this purpose the LPs will establish WP or subnet-steering committees. LPs are specifically responsible for ensuring that the implementations of their WP are consistent with the overall implementation plan and with the other network components. This entails, in particular: i) the continuous monitoring and reporting of the implementation of the tasks within his WP, ii) keeping regularly informed the SC/SNM of progress made in the WP, iii) keeping the SC/SNM informed in a timely fashion of any problems arising therein, and iv) ensuring that the interactions between their respective WP and other network WPs and tasks are consistent with the specifications included in the detailed and overall implementation plan. To this end, LPs will prepare quarterly summary reports (one page, standard format, bullet-pointed style) for SNM and SC (compare section 6).

8.2 Elements of network management

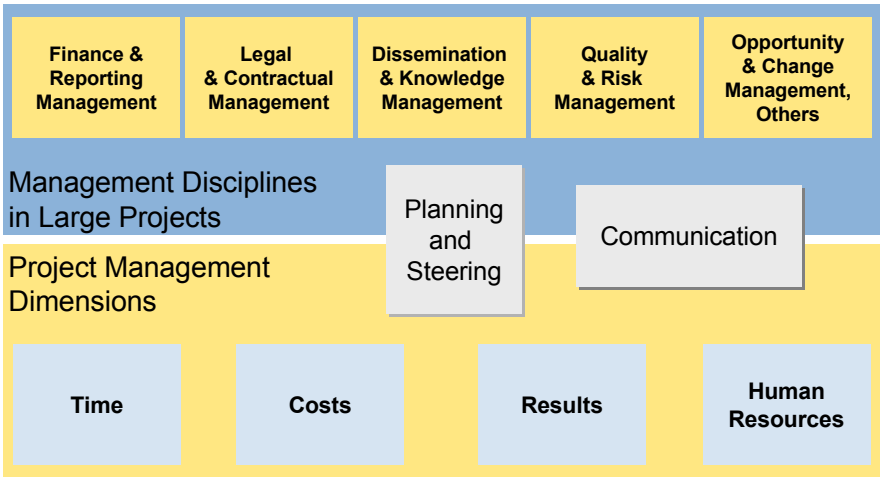

Fig. 12: Management structure

A professional and comprehensive network management adapted to the European Leukemia Net differentiates the elements shown in Fig. 12. The network management organization is straightforward with the mentioned management disciplines reflected in the work package structure of the overall implementation plan described above. The SNM in close collaboration with the NMC is in charge of all management elements in the European Leukemia Net.

Finance and Reporting Management
The objective of the finance management in European Leukemia Net is to organize the whole financial regime of this NOE in a transparent and satisfactory way for all parties. The financial management is based on the overall financial plan, the annual 18 month financial plans and on the payments schedule defined by the EC for NOEs.

Fig. 13 describes the reporting, payments and review schedule for the 5-year project European Leukemia Net. The related administrative part will be carried out by SNM/NMC who will

- ensure that all administrative documents, including cost statements, audit certificates and management-level justification are timely and effectively prepared by each partner,
- prepare the financial report, including the contributions of the partners and a summary financial report, directly in the following month of the reporting period and transmit it to the EC,
- carry out, with no undue delay, all financial tasks necessary to ensure that payments from the EC are effectively forwarded to all partners in line with the approved cost statements. Thus a satisfactory advance payment for each project partner should be guaranteed.
- take care on accounting and book-keeping.

The annual activity reports for each period will be prepared by the SNM in close co-operation with the NC. These reports include a progress statement from each WP, a management-level overview of the activities carried out, the description of progress toward scientific and technological objectives, associated innovation-related activities, scheduled deliverables and milestones as well as the description of problems encountered and corrective action taken.

All financial and activity reports will be controlled by SNM/NC and signed-off by the NC upon approval by the Steering Committee.

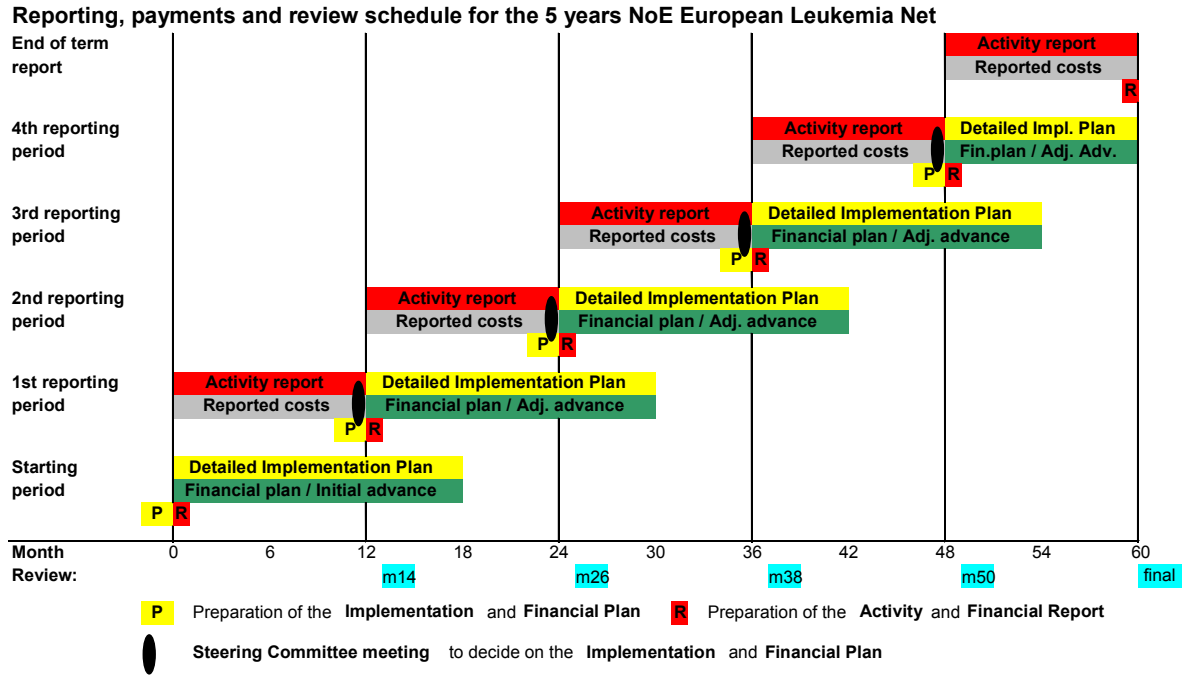

Fig. 13: Financial management

Legal and Contractual Management

Legal and Contractual Management comprises preparation, updating and managing of the Consortium Agreement (CA) between the partners, technology transfer, preparation and announcement of patents, regulation and controlling of intellectual property rights (IPR), integration of SMEs, launching of competitive calls for new partners and an overall contractual monitoring. The Network partners will not form a European Economic Interest Group (EEIG), thus all partners will retain their own legal status. Details of scientific and project management as well as related processes are described in the Network Guide (NG), which is the basis for all work, actions and communication within the European Leukemia Net and constitutes an integral part of the CA. The European Leukemia Net with a high potential of innovative results and products may require specific arrangements concerning IPR and patents.

The CA will include explicit provisions concerning the mechanism for the settling of possible disputes arising between partners, in particular in the case of partner(s) failing to promptly and effectively supply contributions agreed upon and defined in the implementation plan. Internal decision processes are outlined in detail in the CA/NG.

The task and competence matrix in Table 7 shows the main decision paths and organizational units involved. With a clear allocation of roles and responsibilities for tasks and decisions an effective management of the network and handling of issues is guaranteed. The obligation to inform specific groups or to obtain their approval also ensures continuous flows of information and communication.

Table 7: Decision making process within the network

Organization Units / Task	EC	SC	NC	SNM	NMC	WPL	Description/ Decision-making
Contractual management	oa	d	mr	jr		a	unanimous
Alteration in the partnership / consortium agreement		d	mr	jr		jr	
- e.g. new partner							
- changes in roles/resp.		D	mr	q		q	majority
- premature completion/ termination of the NOE	oa	d	mr	jr			unanimous
Acceptance of deliverables		a	d			mr	
Solution finding for escalated mgt. Or scientific problems		d	mr			q	majority
Exploitation of results (e.g. patents, knowledge, prototypes)		d	mr	jr		jr	unanimous
Periodic financial & activity planning	oa	d		mr	jr	jr	majority
Project realization & progress controlling of WPs as per plan		a		mr	jr	s	majority
Ongoing internal network information of all partners about status, news etc.		a	mr	jr		s	
External status reports	oa	a	mr	jr	s	s	
Postponement of milestones		d		mr		q	majority

Decision-making: If 50% of the members of the SC are present in a meeting, the SC is able to decide. The SC takes decisions unanimously or by majority.
Legend: **a**=approval; **oa**=overall approval; **d**=decision; **q**=request; **mr**= main responsible for preparation/planning; **jr**=jointly responsible; **s**=supply, **mgt**=management

During the network term, new partners, especially SMEs, will have to be integrated into the network team. Up to 15% of the overall grant is reserved for this purpose. The integration requires a permanent updating of the CA and a bulk of management efforts to be handled by NC/SNM.
SNM and NMC monitor all contractual issues and report to the SC every half year.

Quality & Risk Management
The three dimensions costs, time and results influence each other and affect network quality, success and achievement of objectives. Every network activity, report or deliverable has to be evaluated in these three dimensions. SNM and NMC will take care of the planning of quality criteria and continuous measurement of their achievement as well as recurring target/actual comparison for all three dimensions. For deliverables a scientific quality process will be organized and implemented. The deliverables have to be checked by two other partners before they can be signed-off by the SC/NC.

Risk Management includes the processes concerned with identifying, analyzing, tracking and controlling the network risks. The risk management for European leukemia net starts at the beginning of the implementation phase and will be carried out consistently throughout the whole network. The goals of Risk management are:

- Early assessment and controlling of the network risks based on a comprehensive risk model
- Increase of transparency regarding existing dependencies (activities, time, resources, costs)
- Development and implementation of mitigation and contingency actions (short-term, medium-term)

The risk management will be carried out by the SNM/NMC.

Opportunity & Change Management, Others
Within the funding period of the NOE, there will be requirements for new opportunities and changes to network goals and results as well as to the network environment.

- Opportunities for improvement or additional benefits will be discussed at the regular SC meetings
- Requests for changes to the network are handled with a formal requirements-change-management process and can be brought to the SC by any full member of the Consortium
- Network-change-management is used to handle changes in the network environment, which affect network stakeholders.
- Changes in external conditions affecting the network have to be identified rapidly by the SNM and corresponding measures have to be derived.
- The network management has to ensure the swift implementation of changes to network results in all WPs (therefore, aspects of change management are an integral part of the communication concept.

Other activities of the SNM with support from the NMC include the overseeing of socio-economic and society issues related to the research activities, the promotion of gender equality and the control of ethical aspects in the project.

8.3 Communication Concept

In principle, the communication shall guarantee, that at any time within the European LeukemiaNet the necessary information is provided promptly and adequately to the different internal and external target groups. The communication objectives are as follows:
Information is provided by the WPs at the right time to the NMC
Formal or official reports/information are approved the SC/NC and provided to ELIC
ELIC provides structured informations to users

The NC is responsible for the communication between the Consortium as a whole and the EC. The SNM plays an essential role in the internal network communication. She is responsible for the actual implementation of all communication flows established among partners, network stakeholders and the public. The NMC supports the communication activities. Mailing lists will be updated and the European leukemia net internet page will be maintained in close collaboration with WP 2 and WP 3. The internet page includes an Intranet for exchange of documents and data inside the network as well as a public part, where news, network information and deliverables are available as far as they are approved by the EC. The **Reporting** issue, as mentioned above, is an important integral part of the network communication. Besides the reporting activities defined by the EC, the internal flow of quarterly progress reports and preliminary deliverables, which are consolidated by the responsible LP and then forwarded to the LP, is of utmost importance for tracking progress and achievement of the overall network objectives.

Meetings
An overview on network and workpackage meetings is shown in Table 8.
A **kick-off symposium** is planned for the whole network in the first month after network start in Heidelberg. To improve the communication flow between all partners, network symposia will be organized at least once every year.
Periodic meetings of the **SC** are planned to take place approximately every three months throughout the funding period. Additional SC meetings may be held according to demand. Annual meetings of the whole Consortium are fixed at the end of each 12 month reporting period (see Finance and Reporting Management).
Technical meetings may be organized to discuss specific issues requiring targeted information exchange and discussion on the level of a work package, or the overall network. Technical sessions can be proposed by any partner, and their actual implementation is subject to a decision by the NC/SNM. Technical sessions are organized by the convening partner, and do not require, in principle, the participation of all partners.

To optimize the use of financial resources, all efforts will be made to combine the dates and venues of technical sessions with those of other network events or to use virtual meetings.

Table 8: Overview of network meetings

Meeting	Participants	Lead	Frequency
Workpackage level **a) WP-steering committee** Goals: Spread information between the WP participants Monitor deliverables and progress of the WP	WP-SC	WP chair(s) (s. legends to fig.10 + 11)	approx. every 3 months
b) WP-participants Goals: Spread information between the WP participants Technical discussions Deliverables, progress of the WP	WP-participants	WP lead participants	approx. every 6 months
Network level **Steering committee meeting** Goals: Overall Status: deliverables, costs, milestones, risks Approval of requests Formal acceptance of deliverables Internal escalation / arbitration Problems Status, status report	SC	NC	approx. every 3 months (virtual meetings possible)
External advisory board meeting Goals: - Public visibility - Second opinion - Open issues	EAB members	EAB Leader	yearly and/or by telephone conference, round mail or virtual
Annual network symposium Goals: - widely spread information and communication in the network	All network members	NC/SNM	yearly

SC: Network Steering Committee, NC: Network Coordinator, LP: Lead Participant, SNM: Scientific Network Manager, EAB: External Advisory Board, WP: work package

Minutes will be taken of all SC meetings and filed appropriately. Decisions and results of WP meetings are documented in a decision protocol.

Network Communication Tools

The following tools and instruments enable an efficient management of the network:

- Network Guide, containing all relevant information on goals, guiding principles and agreements made for the network and the WPs (e.g. consortium agreement)
- The European leukemia net internet page
- Overview of deliverables with a clear statement concerning time, costs, quality, responsibility, content, etc.
- Schedule, containing all activities, milestones, results, network progress, meetings, etc
- Open issue and decision list, which are collected centrally and distributed adequately.
- Overview on expenses (internal and external) for transparent budget controlling.
- Risk log with a central aggregation and tracking of risks.
- Network status reports, documenting progress as well as problems in WPs and the overall network.

9. ETHICAL ISSUES

The proposed research activities involve:	YES	NO
• Human beings	●	
Persons not able to give consent		●
Children		●
Adult healthy volunteers		●
• Human biological samples	●	
Human embryonic stem cells in culture		●
Human fetal tissue / human fetuses		●
• Personal data or genetic information	●	
• Animals (any species)	●	
Transgenic animals	●	
Non - human primates Dogs, pigs, cats		●
• Release into the environment of genetically modified micro-organisms or plants		●

We confirm, that the proposed research does not involve:

- research activity aiming at human cloning for reproductive purposes,
- research activity intended to modify the genetic heritage of human beings which could make such changes heritable
- research activities intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer,
- research involving the use of human embryos or embryonic stem cells with the exception of banked or isolated human embryonic stem cells in culture.

9.1 General Principles

All research performed within the NoE European LeukemiaNet will conform to relevant EU legislation such as:

- The Charter of Fundamental Rights of the EU
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data
- Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC,75/318/EEC and 75/319/EEC on the approximation laid down by law, regulation or administrative action relating to proprietary medicinal products
- Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions
- Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms
- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC

and to International conventions and declarations such as:

- Helsinki Declaration in its latest version
- Convention of the Council of Europe on Human Rights and Biomedicine signed in Oviedo on 4 April 1997, and the Additional Protocol on the Prohibition of Cloning Human Beings signed in Paris on 12 January 1998
- UN Convention on the Rights of the Child
- Universal Declaration on the human genome and human rights adopted by UNESCO

We will take into account the opinions of the European Group of Advisers on the Ethical Implications of Biotechnology (1991 -1997) and the opinions of the European Group on Ethics in Science and New technologies (as from 1998).

In addition, we confirm that if new protocols to the convention on human rights and biomedicine will come into force when the research project starts, they will be respected.

9.2 Ethical Review

All lead participants of the work packages except two in Switzerland are located in EU member states. We do not expect that one of the EU member states or Norway or Switzerland still does not have a competent independent ethics committee /independent regulatory body -(IEC/IRB) to review the research protocols. In addition, the Network Coordinator and his / her staff will take great care to ensure that no research activity within the NoE is initiated without the prior approval of the competent IEC and / or regulatory bodies.

We would like to mention that all physicians of all participating countries are asked by their professional obligation to obey the Declaration of Helsinki in its current version. Ethical and / or regulatory review will be sought in accordance with the legal and ethical requirements in the countries, where the research takes actually place. In any case there will be a review by the competent IEC/IRB in the country of the respective lead participant / principal investigator.

We do not expect that a participant country does not have a competent body for ethical and / or regulatory review. Countries, which cannot guarantee to perform research in accordance with the ethical rules for FP6 will not be allowed to participate in the research activities of this NoE.

9.3 Human samples

Human samples will only be taken and stored after prior written consent by the research subject. There will be complete prior information concerning the purpose (e.g. the type of analyses that will take place) of taking and storage of the human samples including the planned duration of the storage and what happens thereafter. In addition, in non-anonymized human samples the research subject has the right to withdraw his / her consent and to ask for destruction of his / her sample without giving a reason. In clinical trials there will be a separate informed consent form for human samples, and the access to clinical trials will not be limited to those, who have given informed consent to the collection of human samples.

The duration of storage of human samples depends on the research questions. All the necessary information concerning duration of storage and thereafter will be provided in the respective informed consent form. These informed consent forms for human samples will be reviewed by the IEC/IRB, too.

Considering topics C and D of the Ethical Rules for FP6 we would like to emphasize that we will comply with all relevant legal and ethical requirements be it from the EU or the various EU member states.

We will take care that the rights of the research participants will be protected at the highest level. The EU and the ICH GCP provides in detail how research protocols have to be drafted and how ethical issues have to be addressed. As practically all lead participants and principal investigators have taken part in a responsible position in multinational biomedical research including the collection of human samples there is considerable experience available with these ethical issues. As previously mentioned, all biomedical research and all epidemiological research with person-related data will not be started without prior written approval of the competent IECs/IRBs. To check in detail the patient informed consent form and the procedures for attaining informed consent is one of the major tasks of IECs/IRBs. This refers to the informed consent for collecting human samples, too. Thus it is impossible that within this NoE any ethically questionable research takes place.
The network coordinator will enforce and control the compliance with all relevant ethical and regulatory review necessities.

In the UK e.g. all work involving the use of human biological samples is advised to adhere to the guidelines stipulated in the MRC operational and ethical guidelines for the use of human tissue and biological samples in research.

Sweden does not allow establishing biobanks abroad. Coded samples from national biobanks can however be sent abroad for scientific analysis after authorization from regional and national ethics committees. A national biobank can be set up after approval from an ethics committee and after the patient has read a written information and given a written consent. The samples are stored under the responsibility of a university hospital, usually at the department of pathology. The code key is known only by the researchers and a bank responsible person. The samples will be stored for 10-15 years. They are owned by the national CML study groups and cannot be exploited commercially. After biobanking they will be destroyed.

In Germany the group at the Inst. for Med. Informatics, Biometry and Epidemiology (K. Überla) which will carry the operative core of the Central Information and Communication Services (CICS) has been involved in developing a generic conceptual solution for issues related to the treatment of personal data and to bio-banking within the context of medical research networks in Germany. The major characteristics of this generic solution include:

- Acquisition of personal data or biological samples only after free and informed consent.
- Maintenance of separate (in terms of responsibility, location and technical accessibility) central filing systems for patient identification and medical data.
- Retrieval of personal data and/or samples only after review and approval by an independent panel
- Retrieval only of anonymous data and only for scientific purposes.
- Notification of individual participating patients (again, only following review and approval by an independent panel) in the event of a significant medical discovery or development pertinent to a select group of patients, procedures and technical measures for acquisition, quality assurance and data retrieval preventing the re-association of patient identification and medical data by any individuals other than the medical personnel involved locally in the particular patient's treatment or documentation of this treatment.

The generic conceptual solution was derived in consultation with the German government officers responsible for issues related to personal data at the state level (Beauftragte für den Datenschutz). Consensus was achieved that the generic solution satisfies German national regulations. These regulations have set high standards in the past and have recently been modified to fully comply with EU directives.

The generic solution details extensively the organisational and technical measures, including security measures such as cryptographic communication, required in different scenarios of data acquisition. Above all, there is no common pool of patient identification and medical data. These data are maintained in separate filing systems in different places and under the responsibility and control of different individuals, each committed to specific procedures to be formulated in the network's regulations. The filing systems are set up in such a way that no permanent key that might in the long run identify certain subjects ever circulates within the network, thus effectively preventing unwanted traceability. In the case of desired re-identification following approval by an independent panel. the co-operation of the controllers of both filing systems is required.

The generic solution includes provisions to ensure the data subject's rights as laid out in Directive 95/46/EC, specifically with respect to the right of access, rectification, erasure or block. Furthermore, the network assures the erasure or permanent block of any identifying data in the event that the patient chooses to withdraw his/her consent.The generic solution also contains provisions for maintaining bio-banks. At the time of registration, each sample is coded and linked to the centrally filed medical data. Again, any joint retrieval of samples and medical data (patient identities are not communicated to scientists analysing the samples) is subject to review and approval by an independent panel.

The generic conceptual solution will need to be adapted for central filing systems and biomaterial banks in the European LeukemiaNet. For this purpose, WP 3 includes an initial assessment of the existing IT-infrastructure and the requirements incurred by the network's activities. The specific implementation of the generic solution will be based on the results will of this assessment and will have to be verified against pertinent national regulations in the respective Member States. The provisions outlined above and detailed in the generic conceptual solution will in any case be regarded as a minimum standard and will be applied also in those Member States where no specific national regulation is in force. It is not intended to transfer personal data derived in the context of this project outside the EU.

The experience gained in the German network will provide the basis for appropriate solutions in the European LeukemiaNet.

Exemplary copies of patients information forms of the phase I/II trial on pegylated interferon and imatinib and of the CML IV trial are included in the annex. Similar forms are in existence or are being developed for all clinical trials of the NoE and will be presented to the EC in due time.

Data transfer outside the EU is not provided.

Collected personal data will not be used for any commercial purposes.

Pregnant women are excluded.

9.4 Animals

The animals models proposed within the European LeukemiaNet are several murine leukemia models. These have been developed and successfully used by the investigators and include inbred mice (mus musculus) of various genetic backgrounds.

It is one of the objectives of the network to facilitate the exchange and spread of animal models of leukemias in the scientific community. No funding is sought for the actual animal experiments. All currently used animal models of leukemias are avian or mouse models, where leukemias are either induced by retroviral infection, by specific genetic changes or by mutagen treatment. Combinations of these approaches have been used in the past. The most modern leukemia models in mice either make use of the availability of homologous recombination that allows to generate mice with targeted

disruption of single genes or exchange of genetic material. Also, transgenic animals are being generated that are engineered to express leukemia-associated genes in a time- an tissuespecific fashion. Finally, experiments involving the transplantation of ex vivo genetically modified bone marrow are widely performed. As stated above, it is one objective of the network to collect and evaluate as many of these animal models as possible. Therefore, new ideas that will be funded by other sources, cannot be anticipated.

During the process of drug development, the drug candidates will be extensively tested on leukemia cell lines. In order to comply with the principles of reduction, refinement and replacement of animal experiments, great care will be given to make use of alternative ways of testing, in particular by making use of primary patient samples. For example, leukemia cells from patients can be readily cultured in vitro in the presence or absence of drugs. On these leukemia cells, issues of drug screening, drug specificity and drug dosing will be examined. However, leukemia cells adopt artificial growth patterns when cultured in vitro. Therefore, once lead compounds are identified and sufficiently characterized, the final stages of pre-clinical testing include a careful analysis of toxicity and efficacy in animal models. Wherever possible, organs of sacrificed mice will be stored and offered to other investigators within the Network for their analyses. Particular emphasis will be given to this aspect, as the number of mice can be significantly reduced overall by organ sharing.

The assessment of drug pharmacokinetics, pharmacodynamics, drug toxicity and in vivo efficacy absolutely require appropriate animal experimentation. The requirement of these data prior to clinical trials and the potential benefit to leukemia patients justify the defined use of animal experimentation. No in vitro method is currently available that would provide these data with the necessary confidence. The investigators will regularly screen the literature and attend international meetings to identify such strategies.

Animal experiments will be designed as to minimize the number of experiments. In the design of individual experiments, each group will include 10-12 mice, which is a number sufficient to statistically analyse the data with reasonable confidence. Each experiment will be repeated at least once.

The main adverse effects of the mice will be the development of leukemia, which includes fatigue, fevers, susceptibility to infection and bleeding. Moribund mice will be sacrificed to prevent unnecessary suffering. Certain experiments involve sublethal irradiation with subsequent transplantation (i.e. intravenous injection) of bone marrow. Blood will be collected at several time points.

All animal experiments will be submitted to the Animal Experimentation Review Committee of the respective institution. All animal experiments will comply with current national and European regulations and laws.

In Great Britain e.g. the use of animals in scientific procedures is regulated by the Animals (Scientific Procedures) Act 1986, which is widely viewed as the most rigorous piece of legislation of its type in the world. It puts into effect, and in some ways exceeds, European Union Directive 86/609/EEC (regarding the protection of animals used for experimental and other scientific purposes) and offers a high level of protection to animals whilst recognising the need to use animals in medical research, the development of new medicines and scientific testing. It also has sufficient flexibility to allow the latest ideas and technology to be taken into account when deciding whether the use of animals is justified.

9.5 Transgenic animals

For genetically modified organisms (animal or plant) work will follow the guidelines for 'contained use' as detailed in the European Directive 90/219/EEC, later replaced by Directive 98/81/EC and for 'deliberate release' as detailed in the European Directive 90/220/EEC.

The above mentioned issues equally apply to transgenic mice.

They will be used to identify relevant steps in the process of leukemogenesis. The transgenes either facilitate or prevent the development of leukemia. This genetic approach has proven to be a powerful approach in our current understanding of leukemia.

9.6 Conclusion

- There will be no research in co-operation with developing countries.
- Local ethics committee approval is standard. Hard copies are available on request. Ethic votes from the local ethics committees will be obtained before starting clinical trials and will be provided in due course for the commission.
- The applicants will immediately declare conflicts of interest and describe how they will be adressed.
- The planned research will protect the dignity, autonomy, integrity and privacy of persons, biodiversity, protection of the environment, sustainability and animal welfare.