The Current and Future Role of Information Technologies for Childhood Cancer

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Cancer in Children and Adolescents
A Rare Disease

- > 60 different diseases from newborns to teenagers
  (even more if biomarkers are considered!)
- 15,000 new cases each year in Europe!
- 3000 will die each year
- 1 out of 1000 adults aged 18 to 40 is a paediatric cancer survivor

... a significant Public Health Issue
What is special about Paediatric Oncology in Europe?

- EU public specialized centres

- Networking within clinical trial structures since late 60ties
  - 50% of patients treated within trials (phase I to III)
  - 30% of patients treated according to standard within prospective studies
  - Less than 5% of pharma-sponsored trials

- Many high-level research teams dedicated to paediatric tumour biology

A unique situation for an orphan disease!
A Major Academic Effort!

Survival Rates of Children and Young Adults Suffering from Cancer

- > 90% 2020
- 80% today
- <10% < 1960

- acute lymphoblastic leukaemia
- Acute myeloid leukaemia
- Hodgkin lymphomas
- Non-Hodgkin lymphomas
- Nephroblastoma
- Osteosarcomas
- Ewing sarcomas
- Rhabdomyosarcomas
- Brain tumours
- Germ cell tumours
- Neuroblastoma and ganglioneuroblastoma

Source: Forschungskreis Kinderkrebs, with kind support from Prof. U. Creutzig, Kompetenzzentrum Pädiatrische Onkologie und Hämatologie, www.kinderkrebsinfo.de
What have Academic Trials achieved Paediatric Oncology?

- **Contribution with Multi- Institutional /Multinational early trials:**
  - Phase I and Phase II settings
    - An important step in drug development
    - Dose finding and toxicity profile of new drugs
    - Response rates to new drugs and drug combinations

- **Multinational Clinical Phase III trials**
  - Vital for young person diagnosed with cancer
  - Strategic and complex treatment plans
    (Multiple Chemotherapy Cycles - Surgery - Radiation - Immunotherapy)

A quality instrument to optimise treatment, care and outcome!
The New Clinical Trial Regulation & Data Protection
Huge Need for the right balance!

When patient protection may result in major health inequalities

- **Top 5 cancers**
  - large numbers
  - licensed drugs
  - economic interest

- **Personalised Medicine**
  - moderate numbers
  - innovative drugs

- **Orphan diseases**
  - small numbers
  - no economic interest
  - off label drugs
  - trials expensive
  - bureaucratic burden
Clinical Trials

From Central Data Capture ⇒ Remote Data Entry Systems
From Paper ⇒ electronic Case Report Forms
New Data Base Designs and Functionality
Risk based Monitoring and Surveillance

• Investigators brochure (+ updates) or SmPC
• Protocol and amendments (signed)
• Information sheet and consent form (+ updates)
• Financial aspects
• Insurance statements
• Signed agreements between parties
• EC opinion and composition
• MRHA authorisation
• Investigators CVs
• Medical and laboratory tests, including normal ranges
• Medicine labels
• Instructions for medicine use
• Shipping records
• Certificates of analysis
• Decoding procedures
• Master randomisation list
• Monitoring reports (pre-trial, initiation, close-out etc)
• List of persons responsibilities delegated to (+ updates)
• CRFs and corrections
• SAE notifications from investigators and to EC and MRHA
• EC/MRHA annual reports and final reports
• Subject screening log
• Subject identification code list
• Subject enrolment log
• IMP accountability at site
• Record of retained tissues
• Documentation of IMP destruction
• Completed subject identification code list
• Audit certificate
• Clinical study report
High Risk Neuroblastoma Complex Treatments – Top of the Iceberg.....

**HR-NBL-1 / SIOPEN FLOWSHEET**

### INDUCTION:
- **Rapid COJEC**
  - CBDCA
  - VP16
  - VCR
  - CDDP
  - CYC

### MAT/PBSC
- Sx harvest PBSC
- **CBDCA**
  - 750 mg/m²
- **VP16**
  - 175 mg/m²
- **VCR**
  - 1.5 mg/m²

### Staging
- **local MRI / CT /US, mIBG, BM (aspirate/biopsy)**
  - **BM aspirates only / local ultrasound**
- **G - CSF**
  - Neupogen 5 µg/kg

### Drug Treatments
- **CBDCA**
  - 80 mg/m²
- **VCR**
  - 1.5 mg/m²
- **CDDP**
  - 80 mg/m²
- **VP16**
  - 175 mg/m²

### 13-cis retinoic acid PO
- 160 mg/m²/day x 14 days every 4 weeks
  - Ch14.18/CHO IV
  - 20 mg/m²/day x 5 days every 4 weeks

### Days after Start of 13-cis RA
- 0 28 56 84 112 140

### Aldesleukin (IL-2) Treatment: R2 B
- Aldesleukin (IL-2) SC
  - 6 MIU/m²/day x 5 Days every 4 weeks

### Days after Start of 13-cis RA
- 0 28 56 84 112 140

### Days after Start of 13-cis RA
- 0 28 56 84 112 140
Comparing 2 International Treatment Standards in High Risk Neuroblastoma: US (CEM) vs. Europe (BUMEL)

Both previously published, peer reviewed and claimed superior to previous

- Which one is superior? [Plenary Session, ASCO Meeting 2011]

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Events</th>
<th>3-yrs. pEFS</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>BUMEL</td>
<td>281</td>
<td>136</td>
<td>0.49±0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CEM</td>
<td>282</td>
<td>169</td>
<td>0.33±0.03</td>
<td></td>
</tr>
</tbody>
</table>
Toxicity vs. Relapse Rate by Randomized Arm
BUMEL higher treatment efficacy!

Patients
BUMEL 281 12 0.04±0.01 124 0.47±0.03 0.49±0.03
CEM 282 17 0.06±0.01 152 0.60±0.03 0.33±0.03

log-rank . 0.217 . 0.001 0.000
grey's test . 0.325 . 0.004
FP7 “Network of Excellence”
Kick Off January 2011
33 Partners / 11 European Countries
18 WP: 80 Milestones
82 Deliverables
European Network for Cancer Research in Children and Adolescents

Objectives

- Improve both cure and quality of cure of children and adolescents suffering of cancer
- Facilitate access to:
  - Innovative therapies and tailored medicines
  - Standard care across Europe
- Develop biology-guided therapies
- Propose a European Virtual European Institute for Cancer Research in Children and Adolescents
Towards the ENCCA Virtual Institute and fragmentation reduction in clinical and translational research in paediatric and adolescent oncology

- Integration of stakeholders
- Data and tools sharing
- Training and education
- Innovative clinical trial design

- Harmonisation of care for children with cancer in EU
- Harmonised therapeutic strategies and access to drugs
- Referral schemes and easy access to care
- Better quality of life for children and teens
- High qualified and trained clinicians in Europe
The TRANSCAN Call has been published: 'Translational research on tertiary prevention in cancer patients'.

The ERA-NET TRANSCAN Third Joint Transnational Call for Proposals (JTC 2013) has been officially launched on the topic "Translational research on tertiary prevention in cancer patients". ... (more)
European Clinical Research Council
Chairs of European Paediatric Oncology Research Groups

- **CWS** (Cooperative Weichteilsarkom Studiengruppe or Cooperative Soft Tissue Sarcoma Study Group)
- **EBMT** (European Group for bone marrow and stem cell transplantation - Paediatric Working Party)
- **EICNHL** (European Inter-group cooperation on childhood and adolescent Non Hodgkin Lymphoma)
- **I-BFM** (The International BFM Study Group)
- **EHL** (European Hodgkins Consortium)
- **EpSSG** (European Paediatric Soft Tissue Sarcoma Study Group)
- **EURAMOS** (osteosarcoma)
- **SIOPEL** (SIOPE-Epithelial Liver Tumour Study Group)
- **SIOPEN** (SIOP Europe Neuroblastoma Group)
- **ITCC** (Innovative Therapies for Children with Cancer)
- **EWOG-MDS** (myelodysplasia)
- **EURO-E.W.I.N.G.**
- **UK Novel Agents Subgroup**
- **SIOP Brain tumour group**

European Network for Cancer Research in Children and Adolescents
European Clinical Research Council

Chairs of the National Societies of Paediatric Haematology-Oncology in Europe

- **Blue or pink:** European countries with NaPHOS (blue: in EU / pink: non-EU)
- **Dashed countries:** European countries without a NaPHOS
Elements of a Biomedical Research Infrastructure

- Registries
- Biosamples Biobanking
- Secondary Use of Electronic Patient Records
- Literature Knowledge
- Electronic Data Capture
- Trial Data
- Research Services, Pharmacovigilance, Image Management,
- Data/Document Storage
- Security and Identification
- Document/Data Registry
- Data processing/Statistics
What could be a solution for the encca requirements?

This situation is similar to healthcare ...

→ Adoption of a solution based on the Integrating the Healthcare Enterprise (IHE)

www.ihe.net
Integrating the Healthcare Enterprise

- IHE is designed for **interoperability**
- IHE is already **established and approved** in healthcare
- IHE is based on **standards commonly used** in healthcare and biomedical research
- IHE represents a **fully open approach**

- Integration of data
  - document based repository
  - no complete database model needed upfront
  - Takes care of the diversity of data, processes and research questions
  - Well poised for secondary use of data
To allow the exchange of information and the access to the various bio-banks and registries, ENCCA is planning to develop an interface allowing the exchange of information and access to different bio-banks and registries that is in compliance with respective EU data protection laws,
ICT Landscape

Institutional IT Systems

Interoperability Initiatives

Directive 95/46/EC

ELGA-G

Directive 2011/24/EU

National and international Regulations

Health Information Exchange Systems

Directive 1999/5/EC
IHE Profiles

• Healthcare and research share similar needs, e.g.
  – Identity management
  – Security and Auditing
  – Image management
  – Consent management (Heinze O. et al BMC 2011)
  – Notification and update
  – Workflow support
  – ...

• The IHE approach is designed for system-scale interoperability and
  – Sustainability (as standardised as possible)

• A core element is the Cross-Enterprise Document / Data Sharing (XDS) profile
  (one of many available IHE profiles)
XDS Flow and Interactions

1. Sources post document packages to the Repository
to be defined

2. Repository registers the documents metadata and pointer with the Registry
to be bought and set-up

3. Consumers search for documents with specific information
to be adapted or developed

4. Consumers retrieve selected documents from Repository (-ies)
Source of Documents
The encca virtual institute basic solution approach: ABCD-4-E

Advanced Biomedical Collaboration Domain 4 ENCCA
The ENCCA Virtual Institute Portal Approach

- Content Management System (CMS)
- Communication / Conferencing
- Process Support (Workflows) (interactive) Calendar Discussion Boards
- Governance Auditing Statistics
- Profiles Rights Roles

Legend: mostly achieved partly achieved in progress

ENCCA Portal
www.encca.eu

Public Access
Microsoft Accounts
first.last@encca.eu
Organisational Accounts
lync@encca.eu

Collaboration
User Access Point
User Management

IHE-based research infrastructure
Patient registry, document registry, document repository, ...

Trust Third Party
Patient Identity Data

European Network for Cancer Research in Children and Adolescents
ENCCA is developing a strategy to have a unique access point with standardised dataset to existing biobanks and databases, to facilitate data analysis and eventually new studies in paediatric oncology.

Federation of ENCCA biobanking resources is the introduction of a unique patient identifier for every paediatric cancer patient treated.

Unified concept for patient consent forms that is in accordance with national data protection laws in European countries.

The consortium aims at interconnecting existing bio-banks to arrive at a sustainable base for future joint data analysis and research.
Next steps ...

- Setup of a demo / prototype IHE infrastructure

- Implementing a typical use case:
  - short list:
    - Patient Registry
    - Image Management Service
    - Biomaterial Registry
The 3 IT Partners

AIT
AUSTRIAN INSTITUTE OF TECHNOLOGY

CINECA

FORTH
Foundation for Research & Technology, Hellas
Advanced Biomedical Collaboration Domain for ENCCA

- European Patients in clinical trials statistics (AIT)
- Survivorship Passport Generator (CINECA)
- Biomarker Analysis Suite (FORTH)
- Support the development and maintenance of standardised core datasets for selected biobanks and selected clinical trials

**USECASE PORTFOLIO**

- 4 Source Systems
- 3 Consumer Systems
- 3 IT partners involved
The Survivorship Passport

• Riccardo Haupt
• Silvia Caruso
• Francesca Bagnasco

IGG

• Sabine Karner
• Anita Kienesberger

ICCCPO

• Giulia Stabile
• Maurizio Ortali
• Davide Saraceno
• Roberta Amato

CINECA

All partners of:
ENCCA: WP 13
PanCareSurFup: WP6

ICCCPO Meeting of European member groups  – Basel May 25, 2013
<table>
<thead>
<tr>
<th>SURVIVORSHIP PASSPORT</th>
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</thead>
<tbody>
<tr>
<td>Add new passport</td>
</tr>
<tr>
<td>Search passport</td>
</tr>
</tbody>
</table>

- Insert a new, or
- Search for an existing Passport
**Diagnosis**

The survivorship passport

<table>
<thead>
<tr>
<th>N. passport</th>
<th>Initials</th>
<th>Date of Birth</th>
<th>Date of Registration</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IT001201304121011</td>
<td>DOE JHON</td>
<td>21/03/1999</td>
<td>12/04/2013</td>
<td>-</td>
</tr>
</tbody>
</table>

**DIAGNOSIS FORM**

Fields containing * are mandatory.

- **Date of diagnosis**: 21 08 2007 dd/mm/yyyy
- **Primary treatment Center**: This Institution

**DIAGNOSIS**

- **Cancer category**: Ewing tumor and Askin tumor of bone
- **Diagnosis**: Ewing tumor of bone
- **Diagnosis description**: Askin tumor

**SITE**

- **Site description**: Ewing sarcoma

**DETAILS**

- **Laterality**: 

Cancer **category** according to ICCC-3 diagnostic group/division
Summary and Events after elective end of therapy

In case of relapse/progression after first elective end of treatment, a separate form is available.
The survivorship passport

*Data integration options*

- Integration with existing data flows through **standard format** files
- Automatic or on-demand **data import** from local databases to Passport central database
- **Integration** with Clinical Trials databases
- **DB download** for hospitals according to data access rules
- Possibility to develop specific web services for seamless data integration

European Network for Cancer Research in Children and Adolescents
The survivorship passport data flow

- Passport
- Secure Web Access rules
- Passport dedicated database
- Data Input
- Clinical trials databases
- National/ Hospital databases
- Data download
The survivorship passport

Data integration

Data integration options are currently under testing to simplify the passport creation and let it be smoothly integrable among the interested parties.

A first data mapping has been performed against:

- AIEOP ALL 2000 Protocol (Leukemia)
- AIEOP ALL 2009 Protocol (Leukemia)
- EPPSSG (Sarcoma)
# Printable passport available

John Karter

**Passport number:** IT9012010304121012

<table>
<thead>
<tr>
<th>Demographic data</th>
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<tr>
<td>Date of birth</td>
<td>2000</td>
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<tr>
<td>Gender</td>
<td>M</td>
</tr>
<tr>
<td>Place of residence</td>
<td>ZAGGAA</td>
</tr>
<tr>
<td>Contact belonging to</td>
<td>Camillo</td>
</tr>
<tr>
<td>T-MAIL</td>
<td><a href="mailto:karya@camillo.com">karya@camillo.com</a></td>
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</table>

<table>
<thead>
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<th></th>
</tr>
</thead>
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<td>Date of diagnosis</td>
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<tr>
<td>Institution</td>
<td>Casali Clinic - Genna</td>
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<tr>
<td>Cancer category name</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>High risk</td>
<td>Y</td>
</tr>
<tr>
<td>Grade</td>
<td>2</td>
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<table>
<thead>
<tr>
<th>Other diagnoses</th>
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</thead>
<tbody>
<tr>
<td>Predisposing genetic syndromes</td>
<td>N</td>
</tr>
<tr>
<td>Other medical conditions</td>
<td>N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant tumor</td>
<td></td>
</tr>
</tbody>
</table>

The treatment has been executed following:

- **Radiation therapy**
  - Date: from 03/07/2012 to 13/07/2012
  - Site: Heart
  - Total dose: 1860 cGy

<table>
<thead>
<tr>
<th>Other relevant clinical events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant tumor</td>
<td>Fertility preservation</td>
</tr>
</tbody>
</table>

Data are updated to the date of issue of the passport or the date of the last clinical examination certified by the physician.

The passport can be printed and signed by the clinician.
Link to guidelines for follow-up
Clinical Recommendations

- **STRONG recommendation** “is recommended”
- **MODERATE recommendation** “is reasonable”
- **WEAK recommendation** “may be reasonable”
- **NOT TO DO recommendation** “is not recommended”
Providers and women treated with chest radiation should be aware of breast cancer risk.

Breast cancer surveillance **is recommended** for women treated with > 20 Gy chest radiation.

Breast cancer surveillance **is reasonable** for women treated with 10-19 Gy chest radiation based on clinical judgment and considering additional risk factors.

Breast cancer surveillance may be reasonable for women treated with 1-9 Gy based on clinical judgment and considering additional risk factors.
Median time to diagnosis of breast cancer from radiation exposure is 15 to 20 years, with cases being diagnosed as early as 8 years from exposure.

- Initiation of breast cancer surveillance is recommended at age 25 years or ≥ 8 years from radiation (whichever comes last) for women treated with chest radiation.

*Bhatia et al. J Clin Oncol, 2003*
Annual breast cancer surveillance *is recommended* for women treated with chest radiation for at least up to 50 years of age.

Additional breast cancer surveillance (beyond that recommended by national health care systems) in women older than 50 years of age *is reasonable* based on clinical judgment and pending availability of further data.
The Survivorship Passport
Present status and future vision?

- A template for the individual patient at the moment of the elective end of therapies containing standardized and condensed cancer history and relevant therapy information
- Paper and electronic based, potentially including images and other relevant medical source documents.
- To provide advice and guidance on patient-specific long-term follow-up of possible late effects
- **All languages of the EU ⇒ ExPO-r-Net**
- **Integration into future eHealth based platforms & tools for the survivor population allowing life long best possible care based on accurate information and paying tribute to Europe mobility**
Future expansion
Telehealth in Pediatric Hemato-Oncology

- Interactive outpatient care
- Home surveillance of well being in modern treatment settings
- Prolonged ctn. low dose infusion of anti cancer drugs or immunotherapy (basic vital parameters, ..)
- Palliative Care Settings
A harmonised and integrated approach
to the rationale introduction of molecularly targeted treatment in
clinical trials on leukaemia

Task: **Standardised comprehensive diagnostic approaches in leukaemias**

Main achievements:

- **After a comprehensive survey among the partners** of the AIEOP-BFM ALL 2009 trial (AIEOP, BFM-A, BFM-CH, BFM-G, CPH, INS), on cytomorphology, immunophenotyping, cyto- and molecular genetics, MRD, TPMT genotyping and asparaginase monitoring plus several questions regarding infrastructure and biobanking, **diagnostic recommendations (guidelines) for ALL in clinical trials** have been generated and are published on the ENCCA website and on the website of the I-BFM study group ([http://www.bfm-international.org](http://www.bfm-international.org)).

- **Similar recommendations were finalized for AML.**
Task: Establishment of a harmonized pipeline for molecular diagnostics in a European virtual laboratory setting using very high-risk ALL (VHRL) as a model system

• Main achievements:
  • **Scopeland software** has started to be used by German and Swiss AIEOP-BFM ALL study centers and the relapsed ALL trial at Charité.
  • **Agreement on a defined shared dataset on pediatric ALL.**
  • A meta database for interfacing Scopeland and other systems has been set up (**p-BIOSPRE)**, is functional between Scopeland users and close to be functional for interconnecting additional partners.

• **Successful TRANSCAN application (TRANSCALL)**!
A harmonised and integrated approach to the rationale introduction of molecularly targeted treatment in clinical trials on leukaemia.

**Scopeland**

- laboratory infrastructure management system
- developed by Charité and Kiel
- web-based
- GCP-conformity assured
- four main modules:
  - cytomorphology
  - MRD
  - research
  - specimen bank
- generates reports and is fully flexibel
A harmonised and integrated approach to the rationale introduction of molecularly targeted treatment in clinical trials on leukaemia.

Scopeland database
ALL: levels of genetic characterization

Initiation
- ETV6-RUNX1
- BCR-ABL1
- TCF3-PBX1
- Hyperdiploidy

Promotion / Progression
- PAX5, EBF1, IKZF1, BTG1
- CDKN2A/B, TP53, RB1
- CRLF2, JAK2/3, ABL1, PDGFRB, SH2B3, EPOR
- NRAS, KRAS, PTPN11, NF1, FLT3
- CREBBP
- NOTCH1, FBXW7, PTEN

Relapse
- NT5C2, HGPRT,
- CREBBP

- Cell cycle, self-renewal
- Lymphoid differentiation, hematopoiesis

Hereditary genetic variants
- IKZF1, ARID5B, CEBPE, TP53, PTPRJ, PIP4K2A, GATA3

Predisposition syndroms
- Down syndrome,
- BLM, ATM, TP53, NBS1
- PAX5, IKZF1

- Tumor suppressors
- Cytokine receptors, kinases
- Ras signalling
- Epigenetic regulation

Leukemia
Host

- Cytokine receptors, kinases
- Ras signalling
- Epigenetic regulation
Rational targeted treatment of ALL

Leukemia patient → Clinical information

Bone marrow specimen → Routine diagnostics

Preclinical testing → Individualized treatment

Molecular diagnostics
Task: Integration of a molecular diagnostic pipeline with preclinical model systems for molecularly targeted treatment and application of algorithms for identification and prioritisation of molecular targets

Main achievements:

• Continuing joint assessment of molecularly defined entities by several groups (e.g., IKZF1-deleted, CRLF2, ERG, TCF3/HLF) and data merging for joint analyses.

• Further extension of molecularly defined entities which have been amplified in mice (e.g., TCF3/HLF; TCF3/PBX1).
Task: Harmonization and integration of clinical platforms for the introduction of molecularly targeted treatment in leukaemias

- Main achievements:
  - Further development of integrational activities regarding existing biobank data systems of different frontline and secondline clinical trial groups completed (p-BIOSPRE-based).
  - **IntReALL trial platform is functional.**
## ENCCA network of collaboration: FP6 and 7 projects

<table>
<thead>
<tr>
<th>name</th>
<th>Area of collaboration</th>
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| PanCareSurfUp (FP7)         | - European sustainable strategy for clinical trial paediatric oncology.  
- Clinical epidemiology and prospective registries for patients on standardised protocols  
- Quality of survivorship (integration of late effect aspects into the survivorship passport creating personalised and risk based recommended health-checks) |
| CONTRACT (FP7)              | - Informed consent  
- Legal and technical aspects and solution                                                                                                                                                                           |
| EuroCanPlatform (FP7)       | - Bio-banking, e-mobility, training courses, regulatory issues concerning clinical trials, contact with industry.  
- One of the member of the Steering Committee, Ulrik Ringborg, KI, is part of the SAB of ENCCA                                                                 |
| IntReALL (FP7)              | - Improved therapeutic strategies using predictive biomarkers in leukaemias                                                                                                                                              |
| P-MEDICINE (FP7)            | - Integrated clinical research infrastructure                                                                                                                                                                            |
| EUROCOURSE (FP7)            | - Clinical epidemiology and prospective registries for patients on standardised protocols                                                                                                                                 |
| ASSET (FP7)                 | - Integrating clinical trials and tumor biology research in bone sarcoma                                                                                                                                                 |
| EuroBoNeT (FP6)             | - Integrating clinical trials and tumor biology research in bone sarcoma  
- Development of a European Tumor Board for Centralised Local Therapy Planning                                                                                                                                     |
H. Kovar et al., "The First European Interdisciplinary Ewing Sarcoma Research Summit", Frontiers in Paediatric Oncology, 2012

Welcome

PROVABES is a joint proposal of the three leading European Ewing sarcoma study groups: EURO-EWING, the Italian Sarcoma Group (ISG) and the Spanish Sarcoma Group (GEIS).

>>> Kickoff Meeting 15/16th of July in Muenster (DE) <<<

These groups have formed a consortium for collaborating with the leading experts on molecular, cellular and translational Ewing sarcoma (ES) research. Each of these scientists will contribute his or her unique expertise to the validation of prognostically relevant biomarkers of solid tumours.

The majority of European ES patients are treated within clinical trials under the auspices of the clinical trial groups cooperating in this consortium. Owing to multimodal treatment strategies, the progress of translational research is rapid and high-quality results are rapidly obtained. These groups have formed a consortium for collaborating with the leading experts on molecular, cellular and translational Ewing sarcoma (ES) research. Each of these scientists will contribute his or her unique expertise to the validation of prognostically relevant biomarkers of solid tumours.
Concept

Overview on the PROVABES consortium and the respective objectives.

PROVABES PROspective VAliation of Biomarkers in Ewing Sarcoma
European Reference Networks


Directive 2011/24/EU on the application of patients' rights in cross-border healthcare

Enrique Terol MD; PhD, Seconded National Expert. Policy officer
European Commission, DG SANCO
**European Reference Networks (ERN): aim of Article 12:**

(Directive Patient's Rights to Cross border Healthcare)

- **Support the development of European Reference Networks**

- **Improving** access to highly specialised healthcare for patients suffering of diseases and conditions:
  - low prevalence/rare
  - complex and cost-intensive
  - requiring a particular concentration of expertise
European Reference Networks

Network
Rare neuromuscular diseases
(Malattie neuromuscolari rare)

Member
Azienda Ospedaliera Universitaria di Pisa — Italy
Criteria and conditions for Networks

✓ 1. A.1.- have knowledge and expertise to diagnose, follow-up and manage patients with evidence of good outcomes

✓ 1.A.2.- Follow a multi-disciplinary approach

✓ 1.A.3.- Offer a high level of expertise and have the capacity to produce good practice guidelines and to implement outcome measures and quality control

✓ 1.A.4.- Make a contribution to research

✓ 1.A.5.- Organise teaching and training activities

✓ 1.A.6.- Collaborate closely with other centres of expertise and networks at national and international level

Facilitate: cost-effective use of resources

Focusing on: highly specialised healthcare / treatment recognised by international medical science (safety, value and positive clinical outcomes)
**Criteria Healthcare Providers**

**General criteria for all Members in an ERN** *(several sub-criteria for each criteria)*

(a) patients empowerment and centred care

(b) organisational, management and business continuity of the healthcare provider

(c) research and training capacity

(d) **exchange of expertise, information systems and e-health tools**

(e) expertise, good practice, quality, patients safety and evaluation

**Specific Criteria for the Members adapted to the scope of the Network** *(area of expertise, disease or condition)*

(a) competence, experience and outcomes of care

(b) specific human structural and equipment resources and organisation

Based on the evidence and consensus of the scientific, technical and professional community
Telemedicine and other IT solutions and tools are the basis for this project

- Remote guidance and Diagnosis
- Secure exchange of Patient information, databases/registries
- Remote training
- Remote monitoring and follow-up
- Virtual clinical/tumour boards
- Member
- Member
- Member
- Member
- Tele-radiology
- Tele-surgery
- Tele-imaging
- Tele-dermatology
- Tele-consultation
- Local Healthcare Provider
- Local Healthcare Provider
Aim of the exploratory work on the networking dimensions of the Networks

✔ To test and develop a networking organizational model based in multidisciplinarity and cooperation between among the members of the network and with external providers

✔ To implement and analyze the feasibility of the use at EU level of networking tools and IT solutions (virtual boards, transfer of images, e-learning etc..)
European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment (ExPo-re-Net)

2013 12 07 ExPO-r-Net
Call: 4.2.2.7. Pilot networks of cooperation under Directive 2011/24/EU
Key issues addressed by the Directive

**Directive 2011/24/EU of patients' rights in cross-border healthcare**

Focussing on patients' rights & healthcare across the Union:

- **Right to choose and be reimbursed**, under certain circumstances for, healthcare provided by public or private providers located in the EU.

- More **transparency about their rights**, treatment options or, the quality and safety levels of healthcare providers.

- **Strong focus on cooperation among Member States**.

Entry into force at National level 25 October 2013
Kick-Off, Luxemburg March 21st, 2014
18 associated partners and 42 collaborating ones.

<table>
<thead>
<tr>
<th>18 Associated Partners</th>
<th>Name</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRI (Coordinator)</td>
<td>St. Anna Kinderkrebsforschung e.V.</td>
<td>Austria</td>
</tr>
<tr>
<td>SIOPE</td>
<td>European Society of Paediatric Oncology</td>
<td>Belgium</td>
</tr>
<tr>
<td>IGR</td>
<td>Institut Gustave-Roussy</td>
<td>France</td>
</tr>
<tr>
<td>MUL</td>
<td>Medical University of Lublin</td>
<td>Poland</td>
</tr>
<tr>
<td>HULAIFE</td>
<td>Fundación para la Investigación Hospital Universitario La Fe</td>
<td>Spain</td>
</tr>
<tr>
<td>ULUND</td>
<td>Lund University</td>
<td>Sweden</td>
</tr>
<tr>
<td>AOPD</td>
<td>Azienda Ospedaliera di Padova</td>
<td>Italy</td>
</tr>
<tr>
<td>IGG</td>
<td>Istituto Giannina Gaslini</td>
<td>Italy</td>
</tr>
<tr>
<td>CAU</td>
<td>Christian-Albrechts-Universitaet zu Kiel</td>
<td>Germany</td>
</tr>
<tr>
<td>AIT</td>
<td>Austrian Institute of Technology</td>
<td>Austria</td>
</tr>
<tr>
<td>CINECA</td>
<td>Consorzio Interuniversitario</td>
<td>Italy</td>
</tr>
<tr>
<td>INT</td>
<td>Istituto Nazionale dei Tumori</td>
<td>Italy</td>
</tr>
<tr>
<td>KlinikumDo</td>
<td>Klinikum Dortmund GmbH</td>
<td>Germany</td>
</tr>
<tr>
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<td>University College London</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>UOB</td>
<td>Lund University</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>ECRMF</td>
<td>European Cancer Research Managers Foundation</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Charité</td>
<td>Universitätsmedizin Berlin: Charité</td>
<td>Germany</td>
</tr>
<tr>
<td>ÖKKH</td>
<td>Österreichische Kinder-Krebs-Hilfe</td>
<td>Austria</td>
</tr>
</tbody>
</table>
OVERALL AIM:

To reduce the current inequalities in survival by improving the quality of the current healthcare provided across Europe, in particular European countries with lower healthcare.

Link pre-existing reference centres of excellence, seeking mechanism to facilitate movement of information and knowledge rather than patients (ICT tools, e-Health).
SPECIFIC OBJECTIVES:

- Identifying needs of rare childhood and young people cancer types with experts (ECRC).
- Building a Paediatric Oncology ERN–roadmap to identified and certified reference sites and tumour boards.
- Establishment of a Paediatric Oncology tumour board ERN (IT tools –Ehealth)
- Defining the criteria for a common process for identification and certification of paediatric oncolog expert centres in Europe.

- The cross-border dimension of long-term follow-up of childhood cancer survivor in Europe: the survivorship passport.

- Integrating very rare tumors and sof tissue sarcomas into an European reference network.
<table>
<thead>
<tr>
<th>Themes</th>
<th>Project Coordinator Ruth Ladenstein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needs</td>
<td>Coordination</td>
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<tr>
<td>Tumors</td>
<td>Dissemination</td>
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<tr>
<td>Identify</td>
<td>Evaluation</td>
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<td>Survivors</td>
<td></td>
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<tr>
<td>Rare</td>
<td></td>
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<tr>
<td>Tumors</td>
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</table>

The diagram illustrates the themes and their coordinators, with sections dedicated to coordination, dissemination, and evaluation.
# Structure

## 3 Horizontal Work Packages

<table>
<thead>
<tr>
<th></th>
<th><strong>3 Horizontal Work Packages</strong></th>
<th><strong>Leader</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Coordination</strong> of the project</td>
<td>CCRI</td>
</tr>
<tr>
<td>2</td>
<td><strong>Dissemination</strong> of the project</td>
<td>SIOPE</td>
</tr>
<tr>
<td>3</td>
<td><strong>Evaluation</strong> of the project</td>
<td>UOB</td>
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## 5 Core Work Packages

<table>
<thead>
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<th><strong>Leader</strong></th>
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<tr>
<td>4</td>
<td>Addressing needs and challenges of cross-border healthcare co-operations and current expert fragmentation.</td>
<td>CCRI</td>
</tr>
<tr>
<td>5</td>
<td>Paediatric Oncology tumour board ERN based on E-Health and ICT concepts for sharing and providing expert advice.</td>
<td>HULAFE</td>
</tr>
<tr>
<td>6</td>
<td>Defining criteria for a common process for identification and certification of PO expert centres in Europe.</td>
<td>MUL</td>
</tr>
<tr>
<td>7</td>
<td>Cross-border dimension of long-term follow-up: survivorship passport with crucial treatment &amp; followup data.</td>
<td>ULUND</td>
</tr>
<tr>
<td>8</td>
<td>Integrating children with very rare tumours in a European Reference Network.</td>
<td>AOPD</td>
</tr>
</tbody>
</table>
WP 4: CCRI

Addressing needs and challenges of cross-border healthcare co-operations and current expert fragmentation.

- Identifying special therapeutic needs of young people with cancer with experts of the ECTG (ECRC) requiring high expertise interventions (i.e. special surgery, radiotherapy (proton therapy), stem cell transplants).

- Addressing also the challenges (costs, resources, psychological burden and ethical aspects).

- Identify European institution ready to engage as reference centers by establishing a/o rolling out tumor boards.

- Identify European Institutions /hospitals offering top level expertise for special therapeutic interventions

Roadmap for public health care providers and patients
Paediatric Oncology tumour board ERN based on EHealth/ICT concepts for sharing and providing expert advice.

- To develop a strategy to build Expo-r-net TB as tools for providing access to expert care to all European children with cancer in a cross-border setting.
- Implementation of modern IT tool across borders will allow TB to share expert opinions for European children with cancer in need of special cross-border settings.

Expo-r-net Tumor Boards = Hubs of expertise
WP 6: Lublin

To promote high quality patient care in paediatric oncology centres through an internationally recognised system of certification and to reduce inequalities in care among centres and countries.

- Build a Ped O ERN-roadmap to identify and certify reference centers and tumor boards.
- Define the criteria for a common process to achieve those.

Cross-border dimension of long-term follow-up: survivorship passport with crucial treatment & follow-up data.

- To build a virtual paediatric oncology expert reference network for late effects after treatment for cancer in childhood and adolescence

- To translate the Survivorship passport and relevant Guidelines into multiple European languages
WP 8: Padova

Integrating children with very rare tumours in a European Reference Network through the identification and connection of Pediatric Oncology Centres and Cooperative Groups with the necessary expertise with the aim to provide accurate diagnosis and evidence-based treatment to children with VRT in Europe (and worldwide)

Creation of a European Cooperative Group devoted to VRT
VISION: OVERCOME INEQUALITIES IN EUROPE

A huge task and role for Information Technologies to treat Childhood Cancer and to improve outcomes!

Special thanks to IT partner in Clinical Trial Management and European Framework Projects for more than a decade
## Objectives

<table>
<thead>
<tr>
<th>Nb</th>
<th>Title</th>
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<tbody>
<tr>
<td>1</td>
<td><strong>Identifying the needs</strong> of rare childhood and young people cancer types and entity subgroups with experts of the ECTG (ECRC) by addressing also the challenges (costs, resources, psychological burden and ethical aspects).</td>
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<td>Build a <strong>Paediatric Oncology ERN–roadmap</strong> to identified and certified reference sites and tumour boards.</td>
</tr>
<tr>
<td>3</td>
<td>Establishment of a <strong>Paediatric Oncology tumour board ERN</strong> working to common standards and <strong>using IT tools based on E-Hhealth</strong> concepts for sharing and providing expertise and advise.</td>
</tr>
<tr>
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<td>Defining the <strong>criteria for a common process for identification and certification</strong> of paediatric oncology <strong>expert centres in Europe</strong>.</td>
</tr>
<tr>
<td>5</td>
<td>The <strong>cross-border dimension of long-term follow-up</strong> of childhood cancer survivors in Europe: the survivorship passport as an instrument for crucial treatment and follow-up data.</td>
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