Childhood Cancer International EUROPE

European Reference Network for rare or low prevalence complex diseases

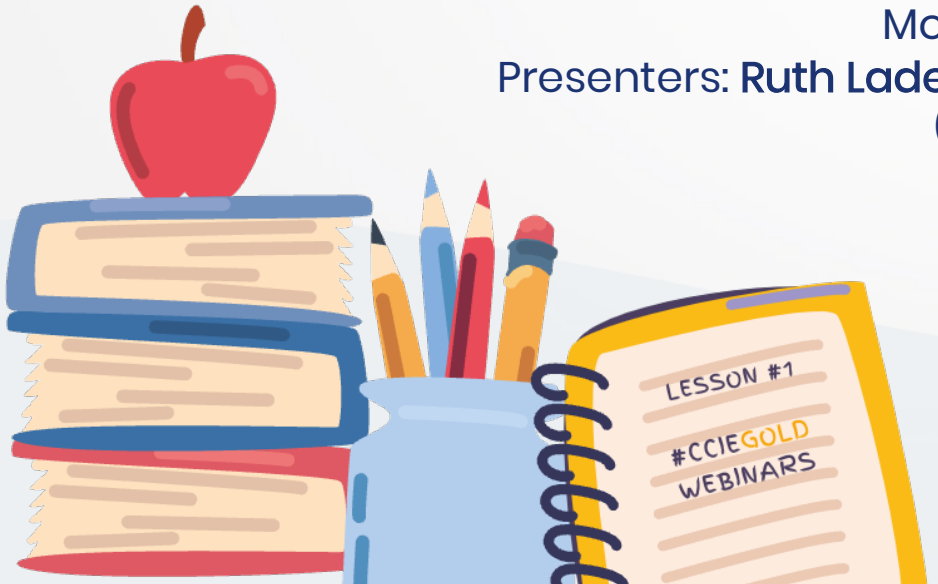
Network Paediatric Cancer (ERN PaedCan)

What is the European Standard of Clinical Practice (ESCP) project?

Advance your knowledge - Gold webinar series

Moderation: **Carina Schneider**, (CCI-E)
Presenters: **Ruth Ladenstein/Martin Schalling**, (ERN PaedCan), **Lejla Kameric** (CCI-E), **Maria Otth** (Young SIOPE)

15.05.2023
17:00 – 18:30 CET



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Childhood Cancer International EUROPE

What is the European Standard of Clinical Practice (ESCP) project?

1. Introduction
2. Patient Advocate's role
3. Showcase brain tumour group

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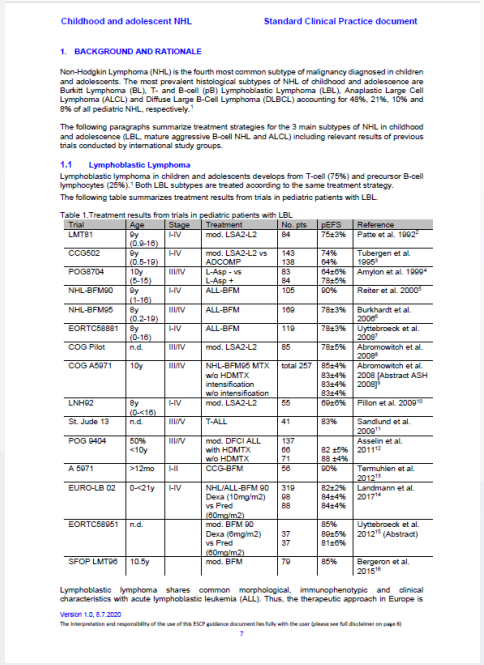
ESCP – whaaaaat?...



1. BACKGROUND AND RATIONALE

Non-Hodgkin Lymphoma (NHL) is the fourth most common subtype of malignancy diagnosed in children and adolescents. The most prevalent histological subtypes of NHL of childhood and adolescence are Burkitt Lymphoma (BL), T- and B-cell (pB) Lymphoblastic Lymphoma (LBL), Anaplastic Large Cell Lymphoma (ALCL) and Diffuse Large B-Cell Lymphoma (DLBCL) accounting for 48%, 21%, 10% and 8% of all pediatric NHL, respectively.[1]

The following paragraphs summarize treatment strategies for the 3 main subtypes of NHL in childhood and adolescence (LBL, mature aggressive B-cell NHL and ALCL) including relevant results of previous trials conducted by international study groups.

1.1 Lymphoblastic Lymphoma

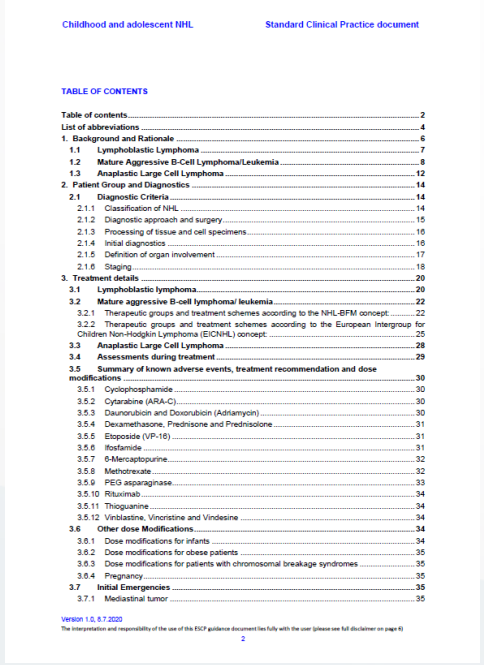
Lymphoblastic lymphoma in children and adolescents develops from T-cell (75%) and precursor B-cell lymphocytes (25%).[1] Both LBL subtypes are treated according to the same treatment strategy.

The following table summarizes treatment results from trials in pediatric patients with LBL.

Table 1.Treatment results from trials in pediatric patients with LBL

Trial	Age	Stage	Treatment	No. pts	pEFS	Reference
LMT81	6y (0.9-16)	I-IV	mod. LSA2-L2	84	75±3%	Patte et al. 1992[2]
CCG502	9y (0.5-19)	I-IV	mod. LSA2-L2 vs ADCOMP	143 138	74% 64%	Tubergen et al. 1995[3]
POG8704	10y (5-15)	III/IV	L-Asp - vs L-Asp +	83 84	64±5% 78±5%	Amylon et al. 1999[4]
NHL-BFM90	6y (1-16)	I-IV	ALL-BFM	105	90%	Reiter et al. 2000[5]
NHL-BFM95	8y (0.2-19)	III/IV	ALL-BFM	169	78±3%	Burkhardt et al. 2006[6]
EORTC58881	8y (0-16)	I-IV	ALL-BFM	119	78±3%	Uyttebroeck et al. 2008[7]
COG Pilot	n.d.	III/IV	mod. LSA2-L2	85	78±5%	Abromowitch et al. 2006[8]
COG A5971	10y	III/IV	NHL-BFM95 MTX w/o HDMTX intensification w/o intensification	total 257	85±4% 83±4% 83±4% 83±4%	Abromowitch et al. 2008 [Abstract ASH 2008][9]
LNH92	8y (0-<16)	I-IV	mod. LSA2-L2	55	69±6%	Pillon et al. 2009[10]
St. Jude 13	n.d.	III/IV	T-ALL	41	83%	Sandlund et al. 2009[11]
POG 9404	50% <10y	III/IV	mod. DFCI ALL with HDMTX w/o HDMTX	137 66 71	82 ±5% 88 ±4%	Asselin et al. 2011[12]
A 5971	>12mo	I-II	CCG-BFM	56	90%	Termuhlen et al. 2012[13]
EURO-LB 02	0-<21y	I-IV	NHL/ALL-BFM 90 Dexa (10mg/m2) vs Pred (60mg/m2)	319 98 88	82±2% 84±4% 84±4%	Landmann et al. 2017[14]
EORTC58951	n.d.		mod. BFM 90 Dexa (6mg/m2) vs Pred (60mg/m2)	37 37	85% 89±5% 81±6%	Uyttebroeck et al. 2012[15] (Abstract)
SFOP LMT96	10.5y		mod. BFM	79	85%	Bergeron et al. 2015[16]

Lymphoblastic lymphoma shares common morphological, immunophenotypic and clinical characteristics with acute lymphoblastic leukemia (ALL). Thus, the therapeutic approach in Europe is



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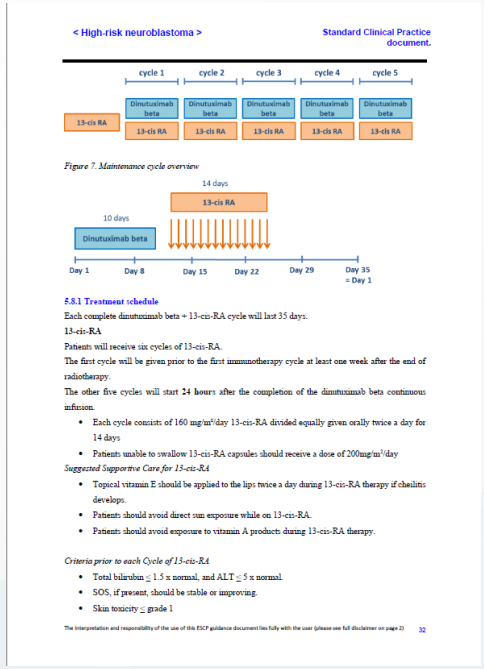


Figure 7. Maintenance cycle overview

5.8.1 Treatment schedule

Each complete dinutuximab beta + 13-cis-RA cycle will last 35 days.

13-cis-RA

Patients will receive six cycles of 13-cis-RA.

The first cycle will be given prior to the first immunotherapy cycle at least one week after the end of radiotherapy.

The other five cycles will start **24 hours** after the completion of the dinutuximab beta continuous infusion.

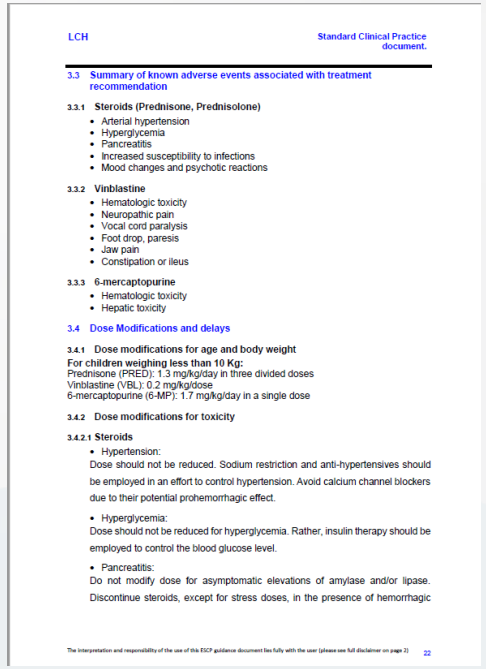
- Each cycle consists of 160 mg/m²/day 13-cis-RA divided equally given orally twice a day for 14 days
- Patients unable to swallow 13-cis-RA capsules should receive a dose of 200mg/m²/day

Suggested Supportive Care for 13-cis-RA

- Topical vitamin E should be applied to the lips twice a day during 13-cis-RA therapy if cheilitis develops.
- Patients should avoid direct sun exposure while on 13-cis-RA.
- Patients should avoid exposure to vitamin A products during 13-cis-RA therapy.

Criteria prior to each Cycle of 13-cis-RA

- Total bilirubin ≤ 1.5 x normal, and ALT ≤ 5 x normal.
- SOS, if present, should be stable or improving.
- Skin toxicity ≤ grade 1



3.3 Summary of known adverse events associated with treatment recommendation

3.3.1 Steroids (Prednisone, Prednisolone)

- Arterial hypertension
- Hyperglycemia
- Pancreatitis
- Increased susceptibility to infections
- Mood changes and psychotic reactions

3.3.2 Vinblastine

- Hematologic toxicity
- Neuropathic pain
- Vocal cord paralysis
- Foot drop, paresis
- Jaw pain
- Constipation or ileus

3.3.3 6-mercaptopurine

- Hematologic toxicity
- Hepatic toxicity

3.4 Dose Modifications and delays

3.4.1 Dose modifications for age and body weight

For children weighing less than 10 Kg:
Prednisone (PRED): 1.3 mg/kg/day in three divided doses
Vinblastine (VBL): 0.2 mg/kg/dose
6-mercaptopurine (6-MP): 1.7 mg/kg/day in a single dose

3.4.2 Dose modifications for toxicity

3.4.2.1 Steroids

- Hypertension:
  Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.
- Hyperglycemia:
  Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.
- Pancreatitis:
  Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic

Question

- **Why do we need ESCPs?**

ESCP Project's Background & Aims

- **BACKGROUND:**
  - **Issue to solve: No harmonised standard treatment recommendations for Paediatric Cancer across Europe outside of often complex randomised front-line protocols**
  - **Launched in October 2019: in an ERN PaedCan and SIOPE CRC stakeholder working session together with parent and patient representatives and colleagues from widening countries.**
- **AIMS**:
  - to develop and approve clinical recommendations reflecting **current best practice for each common childhood cancer type**
  - To provide Europe wide recommendation in all areas where no frontline trials are currently open and shall be updated when new evidence-based standards are established
  - To set the front-line childhood cancer standards and built trust across European landscape
  - To foster collaboration and twinning activities to upscale skills in state-of-the-art diagnostics, medical interventions & care including psychosocial aspects

Question

- **What are they good for?**

Role of the ESCP Documents

1. Foster Equal Standards across Europe

2. To be used when no randomised frontline trial is open in respective countries – whatever the reason

Question

- **Who makes them?**
- **Who is the target group?**

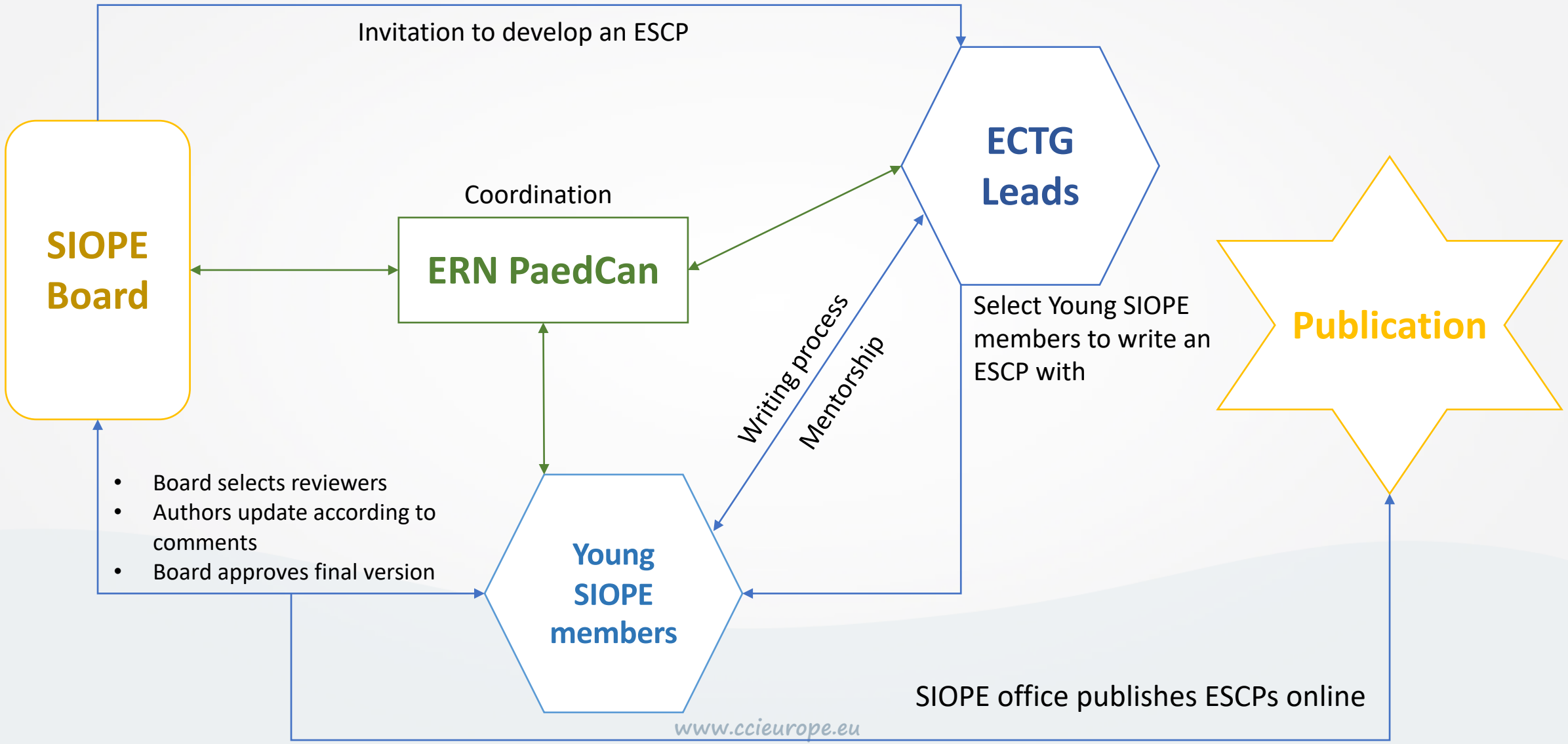
Expectations for the ESCP Project

- **Responsibility and Ownership:**
  remains with the respective European Clinical Trial Group
- **Endorsement:**
  resulting ESCP guidance protocols are being endorsed by SIOPE and ERN PaedCan
- **Benchmark:**
  ESCPs will be of particular value in providing a benchmark for our Widening Countries
- **Transparency and dissemination:**
  the ESCP protocols are being made available online to provide important information to paediatric haemato-oncologists, patients and families in situations where currently, standard best clinical practice is not available
- **Policy:**
  ECSP protocols may become an important tool when negotiating with healthcare decision makers at the national and international level

Question

- **How are they developed?**

ESCP Development Cycle



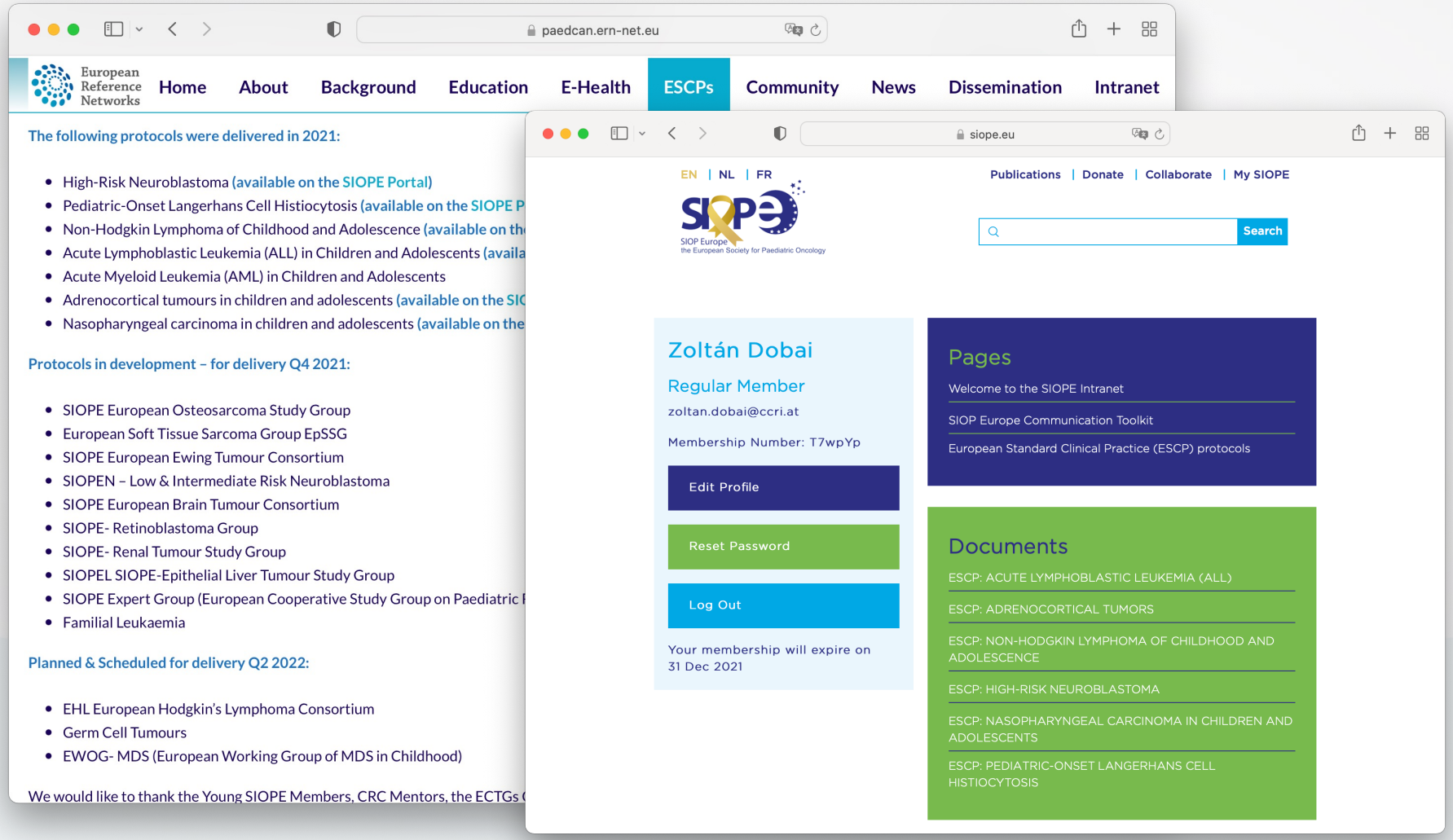
Question

- **How to get access to the ESCPs?**

Achievements

- SIOPE and ERN PaedCan agreed on a disclaimer
  - General disclaimer on the front page of each ESCP to underline that the ESCP guidance documents are not clinical trial protocols and to clarify the responsibility of the users
- SIOPE has developed a secured online solution for making the ESCPs available for the community and the ESCPs which are already online (SIOPE Board review completed)

Password protected access



Question

- **How many are there already?**

Achievement: 23 ESCP launched!

- Acute Lymphoblastic Leukemia (ALL) in Children and Adolescents
- Acute Myeloid Leukemia (AML) in Children and Adolescents
- BTG Overview Document
- Medulloblastoma
- Childhood Intracranial Germ Cell Tumours
- Rare CNS embryonal and sarcomatous tumours and Astroblastoma, MN1-altered
- Ependymoma
- Craniopharyngioma
- Low Grade Glioma
- Advanced intraocular unilateral retinoblastoma: non-conservative management
- Adrenocortical tumours in children and adolescents
- Salivary Gland Carcinoma in Children and Adolescents
- Nasopharyngeal carcinoma in children and adolescents
- Pleuropulmonary Blastoma in Children and Adolescents
- NUT carcinoma
- Osteosarcoma
- Standard Clinical Practice Recommendations for Ewing Sarcoma
- Pediatric-Onset Langerhans Cell Histiocytosis
- European Standard Clinical Practice Recommendations for Non-Hodgkin Lymphoma of Childhood and Adolescence
- High-Risk Neuroblastoma
- Low-risk NBL
- Rhabdomyosarcoma
- Towards European Standard Clinical Practice (ESCP) guidance for individuals with familial leukemia

- 2021
- 2022
- 2023

Question

- **How can patient advocates become aware and familiar with individual ESCPs?**

ESCP Webinars

- Initiated by Andishe Attarbaschi and Ruth Ladenstein as part of the ERN PaedCan Educational Program
- The ESCP webinars accompany the ESCP documents
- They provide a summary of the information contained within them

Format

- Duration approx. 1 hour, incl. Q&A/discussion round
- Presented by Young SIOPE colleagues and senior author
- The webinars are open to everyone for registration
- No fees are implemented
- Targeted at physicians who would like to get an introduction to the ESCP documents

Availability

- The recordings of previous webinars, the slides and registration for upcoming webinars are available on the ERN PaedCan website

https://paedcan.ern-net.eu/the-escp-project/escp-webinars/

Availability

- Acute Lymphoblastic Leukemia
  - Presented by: Mirella Ampatzidou (Greece), Giasomo Gotti (Italy) and Janine Stutterheim (The Netherlands), Mentors Carmelo Rizzary (Italy) and Tomasz Szczepanski (Poland)
- High-Risk Neuroblastoma
  - Presented by: Claudia Pasqualini (France), Mentor Ruth Ladenstein (Austria)
- Nasopharyngeal Carcinoma
  - Presented by: Tristan Römer (Germany), Mentor Tal Ben-Ami (Israel)
- Medulloblastoma
  - Presented by: Inês Alves (Portugal) and Sandra Jacobs (Belgium), Mentor Simon Bailey (UK)
- Adrenocortical Tumours
  - Presented by: Marta Martos Rodriguez (Spain) and Paraskevi Panagopolou (Greece), Mentor Calogero Virgone (Italy)
- Pleuropulmonary Blastoma
  - Presented by: Maria Kourti (Greece) and Arianna Tagarelli (Italy), Metor Gianni Bisogno (Italy)
- Non-Hodgkin Lymphoma
  - Presented by:Vasiliki Tzotzola (Greece) and Paula Perez (Spain), Mentor Andishe Attarbaschi (Austria)
- Langerhans Cell Histiocytosis
  - Presented by: Karel Svojgr (Czechia), Mentor Milen Minkov (Austria)

Question

- **Is there anything else important around ESCPs?**

ESCP Registry

This registry was developed to capture data regarding the use and impact of European Standard Clinical Practice (ESCP) Guidance Documents across Europe, especially in Widening Countries*. It captures data on the availability of treatment protocols and drugs recommended in the ESCP guidance documents.

Data entered in this registry is pseudonymized via the most up to date version of the EUPID system and not publicly searchable. Adherence to the most up-to date security standards is a core tenant of this project.

No patient-identifying data is stored in this registry.

The data will be stored in secured data hosting centres, located within Europe.

**Widening countries as defined in HORIZON2020: Bulgaria, Croatia, Cyprus, Czechia, Estonia, Greece, Hungary, Latvia, Lithuania, Malta, Poland, Portugal, Romania, Slovakia and Slovenia*

ESCP Registry

- The expected number of participating centers is approximately 340, from geographical Europe. All institutions, which treat childhood cancer cases, will be able to participate.
- The registry should not be competing with randomized clinical trials
- A rough estimate would put the number of patients to be included at around 4000-8000*

*based on cancer incidence rates from the European Cancer Information System ECIS

Question

- **What´s next?**

ESCP Registry

- Ready for release (pending final validation checks)
- Specific modules available at release:
  - Acute Lymphoblastic Leukemia
  - CNS Germ Cell Tumour
  - High Risk Neuroblastoma
  - Langerhans Cell Histiocytosis
  - Medulloblastoma
  - Non-Hodgkin Lymphoma
  - Retinoblastoma
  - Craniopharyngioma
  - Adrenocortical Tumors
  - Salivary Gland Carcinoma
  - Nasopharyngeal Carcinoma
  - Pleuropulmonary Blastoma
  - Low-risk Neuroblastoma
  - NUT carcinoma

Thank you!

2 Questions for Lejla

- **How can patient advocates contribute to the ESCP project?**

→To disseminate and give feedback to the ESCPs

2 Questions for Lejla

- **What is their specific role?**

→As reviewers, patient advocates are part of the ESCP development cycle

2 Questions for Lejla

- **Why is it important that also patient advocates are aware of the ESCPs?**

→ to make sure physicians locally are aware and using it (as tool to support them in their work); patient advocates need to understand them so we can support families if they have questions reg. the treatment protocols/procedures

2 Questions for Lejla

- **Are ESCPs accessible to patients?**

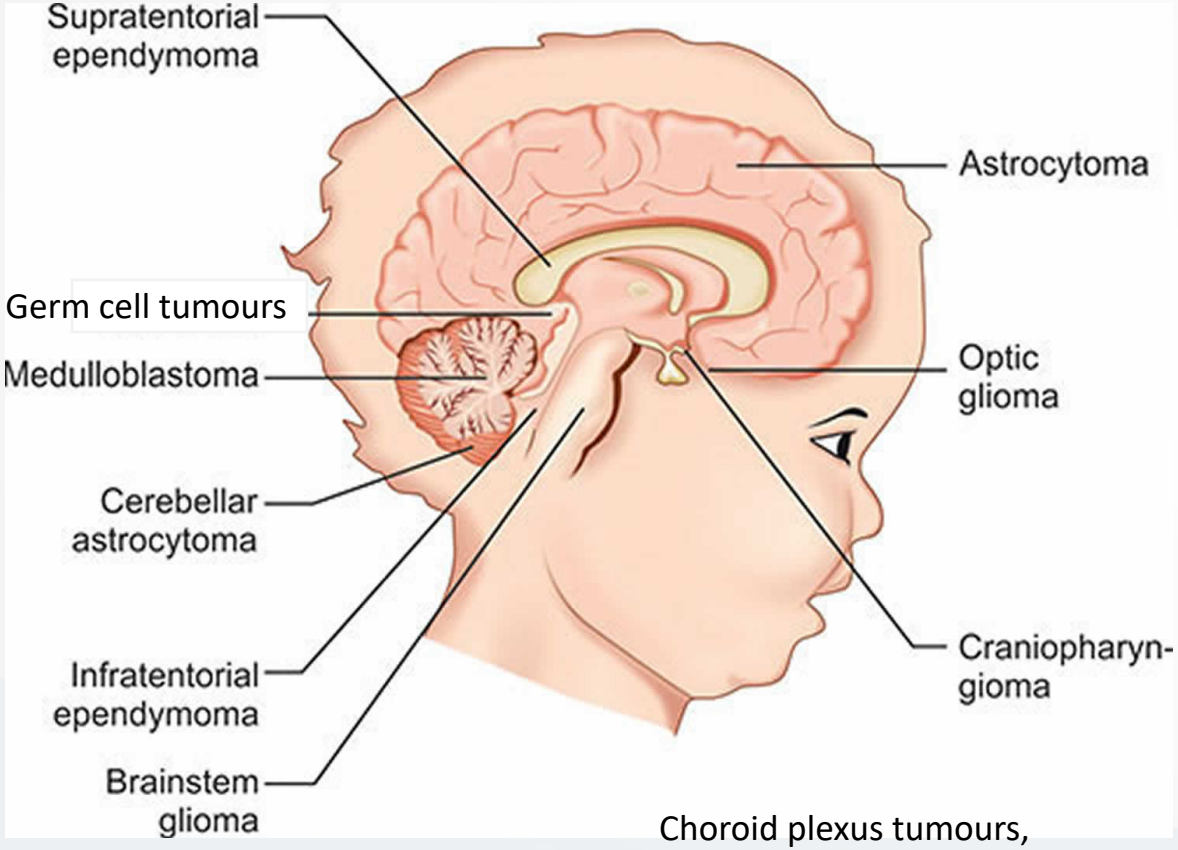
→Not to individual patients, but to specific patient advocates (ePAGs, National Contact Points within ERN PaedCan)

Thank you!

Question to Maria

- **Can you please explain how a new ESCP is created, what is in it, and how to apply it using the Brain Tumor example.**

ESCPs of the Brain Tumour Group (BTG)



Spinal tumours: ependymoma, low grade glioma

Choroid plexus tumours, pnieoblastoma, high grade glioma, rare embryonal and sarcomatous tumours

1. General roadmap
2. Entity-specific guidelines

ESCP BTG – Members

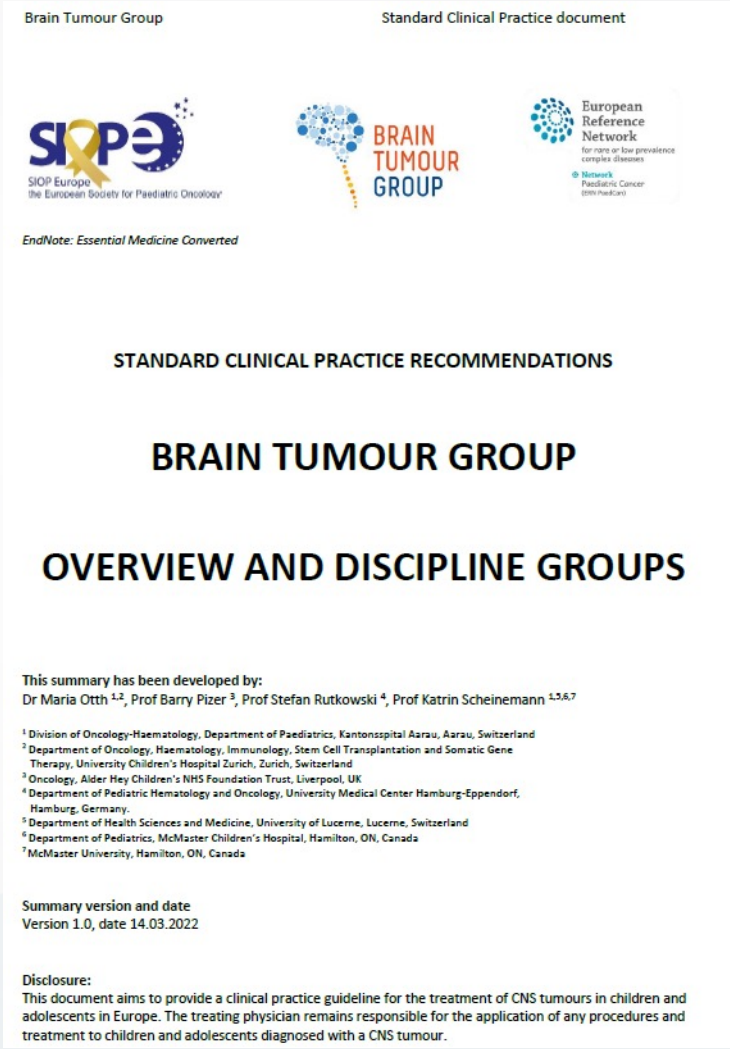
- Steering committee
  - Barry Pizer (UK)
  - Stefan Rutkowski (GE)
  - Katrin Scheinemann (CH)
  - Maria Otth (CH)

- 1-5 Experts of each tumour working group
- 2-4 Young SIOPE members

ESCP BTG – General Roadmap

Guidance and “must haves” valid for all entities

- Background and rationale
- Discipline Working Groups



Brain Tumour Group Standard Clinical Practice document

SIOPE SIOP Europe the European Society for Paediatric Oncology

BRAIN TUMOUR GROUP

European Reference Network for rare or low prevalence complex diseases

Network Paediatric Cancer

EndNote: Essential Medicine Converted

STANDARD CLINICAL PRACTICE RECOMMENDATIONS

BRAIN TUMOUR GROUP

OVERVIEW AND DISCIPLINE GROUPS

This summary has been developed by:
Dr Maria Otth [1,2], Prof Barry Pizer [3], Prof Stefan Rutkowski [4], Prof Katrin Scheinemann [1,5,6,7]

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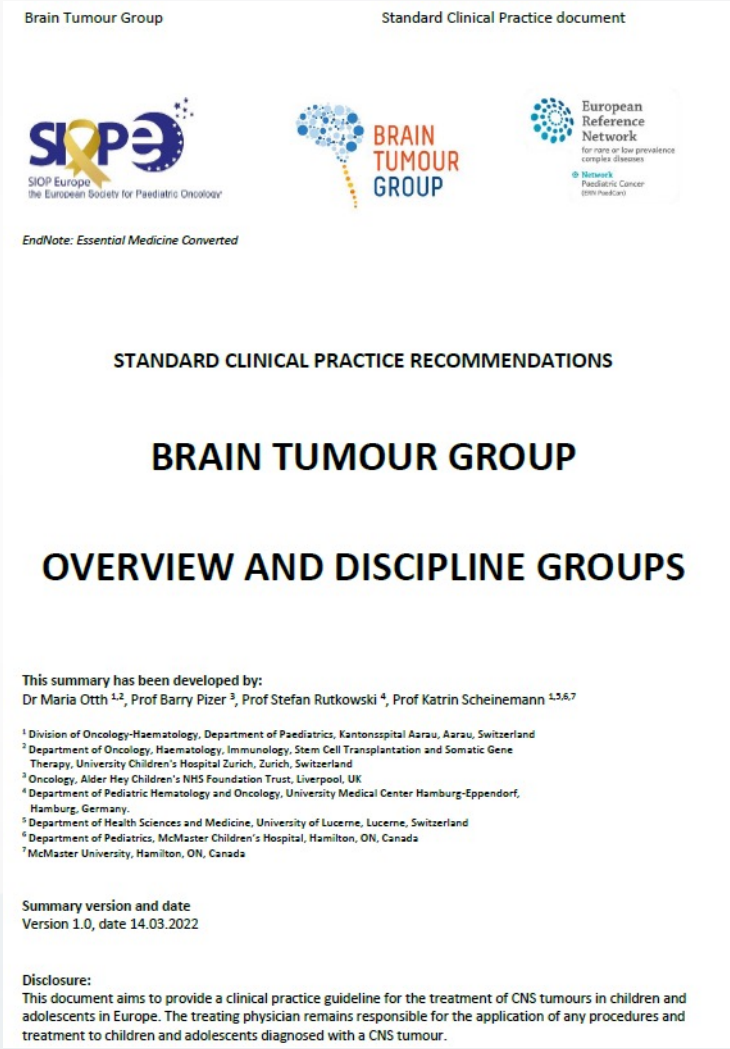
Summary version and date
Version 1.0, date 14.03.2022

Disclosure:
This document aims to provide a clinical practice guideline for the treatment of CNS tumours in children and adolescents in Europe. The treating physician remains responsible for the application of any procedures and treatment to children and adolescents diagnosed with a CNS tumour.

ESCP BTG – Disciplines

- Imaging
- Neurosurgery
- Neuropathology
- Radiotherapy
- Endocrinology
- Neuroophthalmology
- Quality of Survival



Brain Tumour Group Standard Clinical Practice document

SIOP Europe
the European Society for Paediatric Oncology

BRAIN TUMOUR GROUP

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer

EndNote: Essential Medicine Converted

STANDARD CLINICAL PRACTICE RECOMMENDATIONS

BRAIN TUMOUR GROUP

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ESCP BTG – Content of Disciplines

- Background
- Role in paediatric oncology
- Institutional requirements
- Essential quality parameters
- Contact centers/ networks
- Summary

- *Individual sub-chapters*

Summary

(The below mentioned table just serves as an example and is not complete)

Must have
All imaging must be performed according to the SIOPE-BTG neuroimaging protocol
Pre-OP MRI plus contrast must be available for all patients
Early post-OP MRI plus contrast must be available for all patients within 72h post-OP even in ventilated patients
Desirable
Don't do
Do not use CT for standard brain imaging in any childhood cancer tumour

ESCP BTG – Entity-specific guidelines

- Low grade glioma
- High grade glioma
- Medulloblastoma
- Craniopharyngioma
- Germ cell tumors
- Ependymoma
- ATRT
- Choroid plexus tumours
- Pineoblastoma
- Rare embryonal and sarcomaous tumors

ESCP BTG – Content of Working Groups

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ESCP BTG – Output

- General roadmap
- 6 (8)/10 Standard of Care documents available
  - Low grade glioma
  - High grade glioma
  - Medulloblastoma
  - Craniopharyngioma
  - Germ cell tumors
  - Ependymoma
  - ATRT
  - Choroid plexus tumours
  - Pineoblastoma
  - Rare embryonal and sarcomaous tumors

- EJC PO as series → publicly available

Take home messages

- The ESCP Project aims to develop approved clinical recommendations that reflect current best practices for each common childhood cancer type.
- The goal is to improve outcomes and increase childhood cancer survival, and quality of life by providing these benchmarks for best practice with a written recommendation for best standard treatments that can be used as a benchmark where no national recommendations or clinical trial options are available.
- These expert-endorsed recommendations aim to improve access to best standard treatments for all children with cancer throughout Europe and hold the potential of reducing inequalities in childhood cancer outcomes across Member States.
- Patient Advocates have a key-role
    - Give feedback on new ESCPs from the patient perspective
    - Advocate locally for implementation of ESCPs in treatment centres
    - help ensure proper use of the ESCPs in their countries
- Patient Advocates have to be familiar with ESCPs to support families in case they have questions

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Any further questions?

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Gold Webinar: Advance your knowledge - What are ESCPs?

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