Successful Academic Clinical Trials in Rare Diseases can be Valuable also for Common Diseases: Examples and Implementation

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  - The Children's Cancer Foundation of Sweden
  - Stockholm County Council (ALF)
  - The Swedish Cancer Society
  - The Cancer- and Allergy Foundation
  - European Commission
  - European Public Health Executive Agency
  - Karolinska Institutet

My background – Clinician & Clinical Scientist

- Pediatrician
  - → Focus on hematology and oncology
  - → Regularly meet and care for patients with rare diseases (RD)

- Impressed by previous collaborative efforts in pediatric hematol-oncol
  - → International Society of Pediatric Oncology (SIOP), late 1960s.
  - → Nordic Organisation for Pediatric Hematology and Oncology, late 1960s.

Improved survival in childhood cancer

- **We can now <u>cure</u> around 75% of <u>all</u> children with cancer.**
- This is mainly the result of collaborative studies among academic researchers.
- We mainly use chemotherapy, surgery and irradiation.
- Note: The drugs we use are **old drugs**, used in novel combinations.
- Almost all these studies have been academia driven, and usually international efforts (as within SIOP)

Improved survival in Acute Lymphoblastic Leukemia (in Sweden)

- **The most important reasons for the success:**
  - → **Clinical research**
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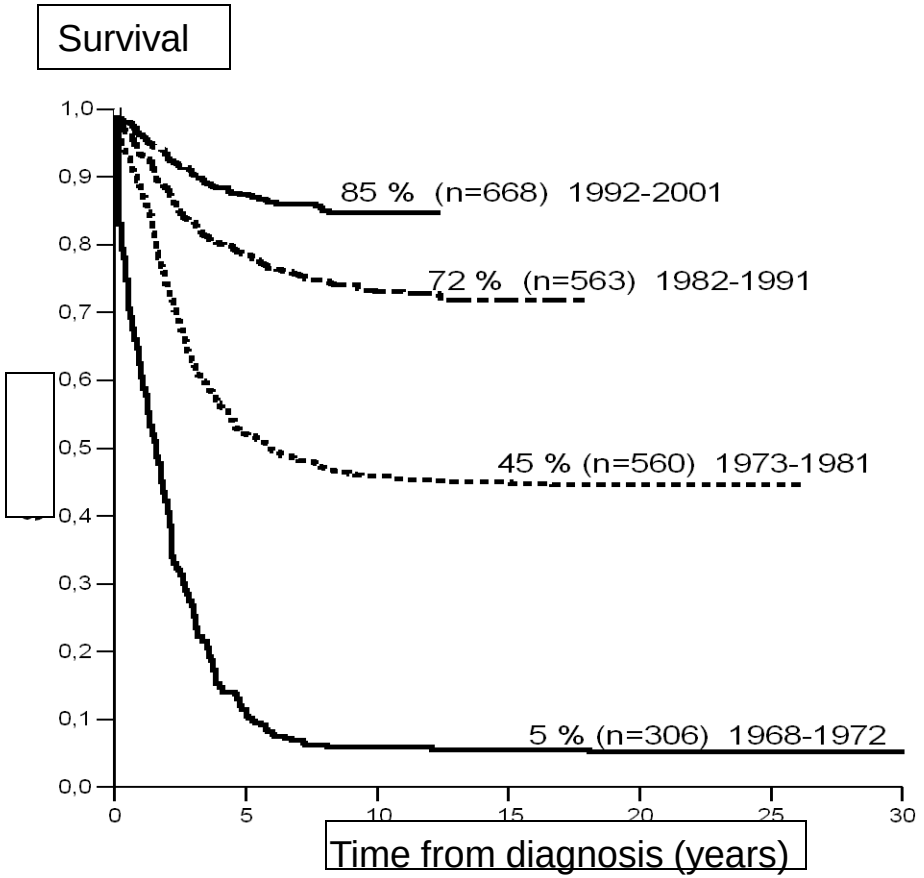
- Hard work = Step by Step, Stone by Stone, Patient by Patient.
- Collaborative academic international studies



Courtesy: Göran Gustafsson, Karolinska Institutet

Clinical Science is Essential in Rare Diseases

Clinical Science can:

- Identify clinical syndromes
- Develop diagnostic tools (essential for proper therapy)
  → Improve patient monitoring
- Improve therapies with existing drugs
  → Run clinical trials
  → Find new indications for old drugs
- Identify new treatments and new potential drugs

Rare Diseases - Challenges

Challenges – personal experiences: Familial Hemophagocytic Lymphohistiocytosis

- Winter 1985-86:
  7 children at our hospital !
- Not in the textbooks!
- Rapidly fatal
- Pathophysiology unknown

Some questions initially asked …

1. **Is FHL more common than presumed?**
2. **Can we define how to make the diagnosis?**

3. Can it be treated, and can it be cured?

4. Can we find out what causes the symptoms?
5. Can we find the underlying cause?

6. Can we learn something about healthy humans?

HLH – Diagnostic Guidelines 1991

- Fever
- Splenomegaly (usually with hepatomegaly)

- Cytopenia (≥ 2 lineages) (Hb <90 g/L, ANC <1.0, platelets <100)
- Hypertriglyceridemia or Hypofibrinogenemia

- Hemophagocytosis

Henter et al. Semin Oncol 1991; 18: 29-33

Some questions initially asked …

1. Is HLH more common than presumed? YES
2. Can we define how to make the diagnosis? YES

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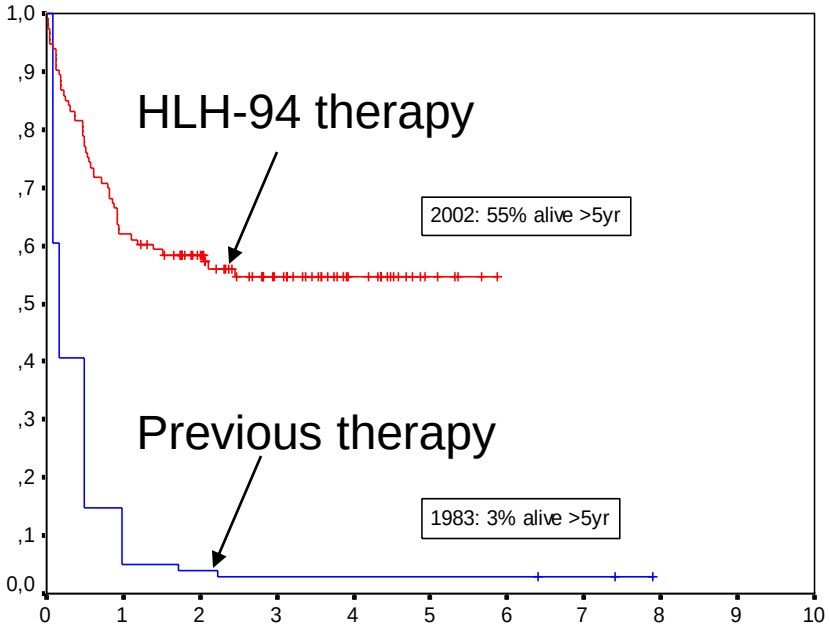
Improved survival in HLH (Hemophagocytic Lymphohistiocytosis)

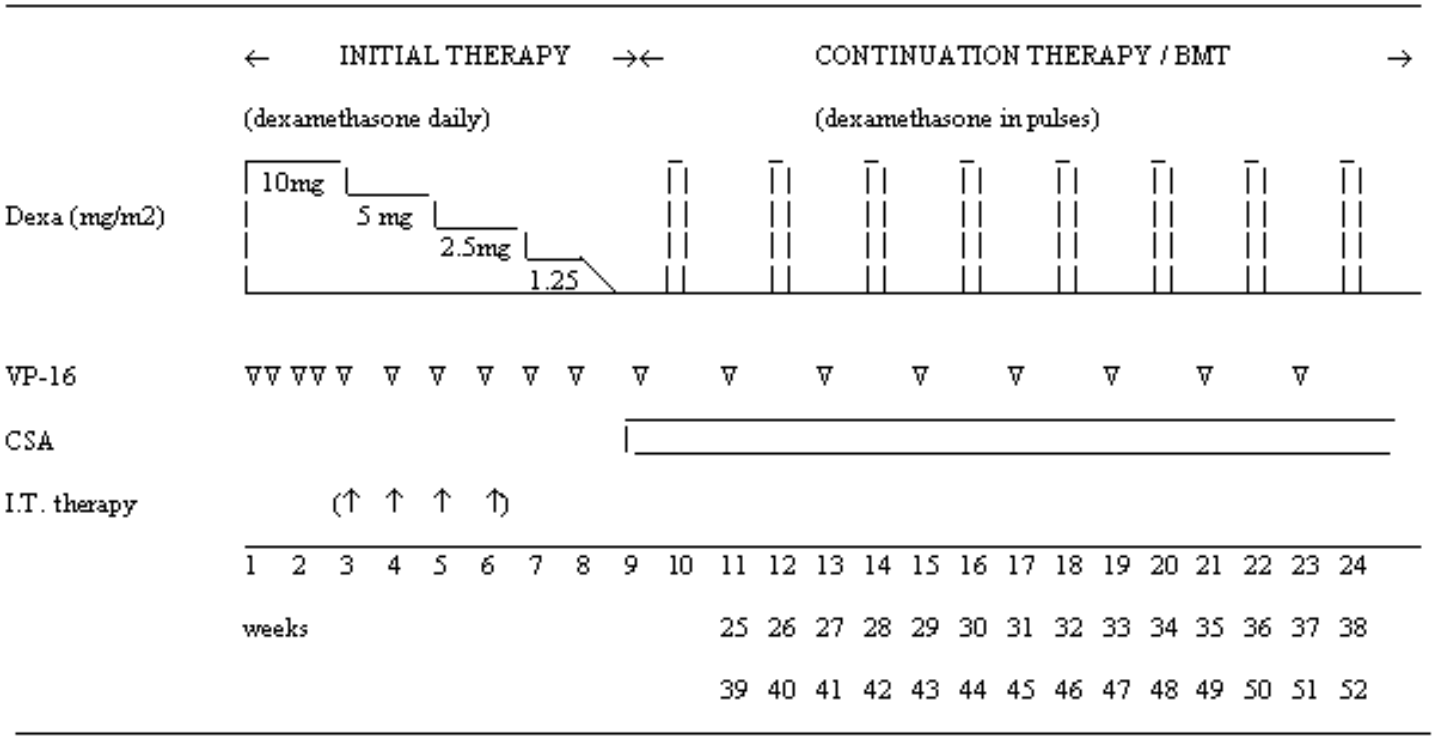
- **Familial hemophagocytic lymphohistiocytosis (familial HLH)**
- Immune defect
  - → Defect immune down-regulation
  - → Typically rapidly fatal
- Markedly improved survival
  - → From 0% to around 50%
- HLH-94: An international collaborative academic study in >20 countries



1983-data: Janka, Eur J Pediatr 1983; 140: 221-230

2002-data: Henter et al. Blood 2002; 100: 2367-2373

HLH-94 treatment protocol



Henter et al, Blood 2002; 100: 2367-2373

Evaluated pat (n=232, from 26 countries)

Germany	**49**	
United Kingdom	**22**	
Italy	**22**	
Scandinavia (Sweden 7, Denmark 4, Norway 3, Finland 1, Iceland 1)	**16**	**66% EU**
Benelux (the Netherlands)	**9**	
Other Europe (Austria 9, Switzerland 2, Czech Rep 1, Turkey 10, Spain 6, Yugoslavia 6, Slovenia 1)	**35**	
North-America (USA 18, Canada 2)	**20**	**11% AM**
South-America (Argentina)	**5**	
Japan	**43**	**22% AS**
Other Asia (Saudi-Arabia 3, Oman 4, Korea 1, Hong-Kong 1)	**9**	
Africa (South-Africa)	**1**	**1 %**
Australia	**1**	
	232	

Some questions initially asked …

1. Is HLH more common than presumed? YES
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5. **Can we find the underlying cause?**

6. **Can we learn something about healthy humans?**

HLH lessons on immune system regulation

- 1) Familial HLH = defect immune regulation (apoptosis deficiency).
  Fadeel et al. Br J Haematol 1999;106:406-15.

- 2) The perforin system that is deficient in FHL, is central in human immune regulation.
  Stepp et al. Science 1999; 286:1957-59.

- 3) CENTRAL FUNCTIONS:
- Downregulate the immune system
- Eliminate virus infected cells
- Eliminate cancer transformed cells

Some questions initially asked …

1. Is HLH more common than presumed? YES
2. Can we define how to make the diagnosis? YES

3. Can it be treated, and can it be cured? YES

4. Can we find out what causes the symptoms? YES
5. Can we find the underlying cause? YES

6. Can we learn something about healthy humans? YES

Secondary HLH

- **An expanding field !**

- Virus-associated HLH
- Bacteria-associated HLH

- Malignancy-associated HLH
- Rheuma-associated HLH
  → Macrophage activating syndrome (MAS)

Bacterial HLH

Baby H: Born 24th week, BW 732g

- 1-mo: *Serratia marcescens* septicemia.

- Also hyperbili (conj), max 916 µmol/L = 54 mg/dL.
- Hepatosplenomegaly, cytopenias (plat $4x10^9$/L). High TG, low fibrinogen. Ferritin >20.000 µg/L.
- No bone marrow investigated for hemophagocytosis. No HLH mutations in the *STX11* or *PRF1* genes.

- HLH therapy (no CSA, immature kidneys), improved rapidly. Recovered fully from the HLH.
- Developed a severe Retinopathy of the Prematurity (ROP), with severe sequelae. No signs of HLH.

Edner et al, Acta Paediatr 2007; 96: 1703-1706

Hypothesis

Cytotoxic therapy for severe avian influenza A (H5N1) infection

Jan-Inge Henter, Chun-Bong Chow, Chi-Wai Leung, Yu-Lung Lau

Lancet 2006; 367: 870–73

The mortality rate in documented avian influenza A virus subtype H5N1 infection is still high, which is currently reported by WHO at about 50%. Post-mortem analyses in affected patients have revealed haemophagocytosis similar to that found in patients with haemophagocytic lymphohistiocytosis (HLH); such haemophagocytosis could be a very prominent post-mortem feature in H5N1 infection. There are also clinical similarities between H5N1 infection and HLH, such as massive hypercytokinaemia, cytopenia, and acute encephalitis. Importantly, patients with another severe viral infection that may be complicated by secondary HLH, severe Epstein-Barr-virus-associated HLH, have significantly better survival if specific HLH therapy (including the cytotoxic and pro-apoptotic drug etoposide) is initiated early, with survival reported to rise from about 50% to 90%. With this notable improvement in survival, specific HLH treatment, including cytotoxic therapy, could be considered in patients with severe avian influenza A infection complicated by secondary HLH.

Case Report

Cytotoxic therapy for severe swine flu A/H1N1

Jan-Inge Henter, Kajsa Palmkvist-Kaijser, Bernhard Holzgraefe, Yenan T Bryceson, Kenneth Palmér

Lancet 2010; 376: 2116

Cytotoxic therapy for severe swine flu A/H1N1

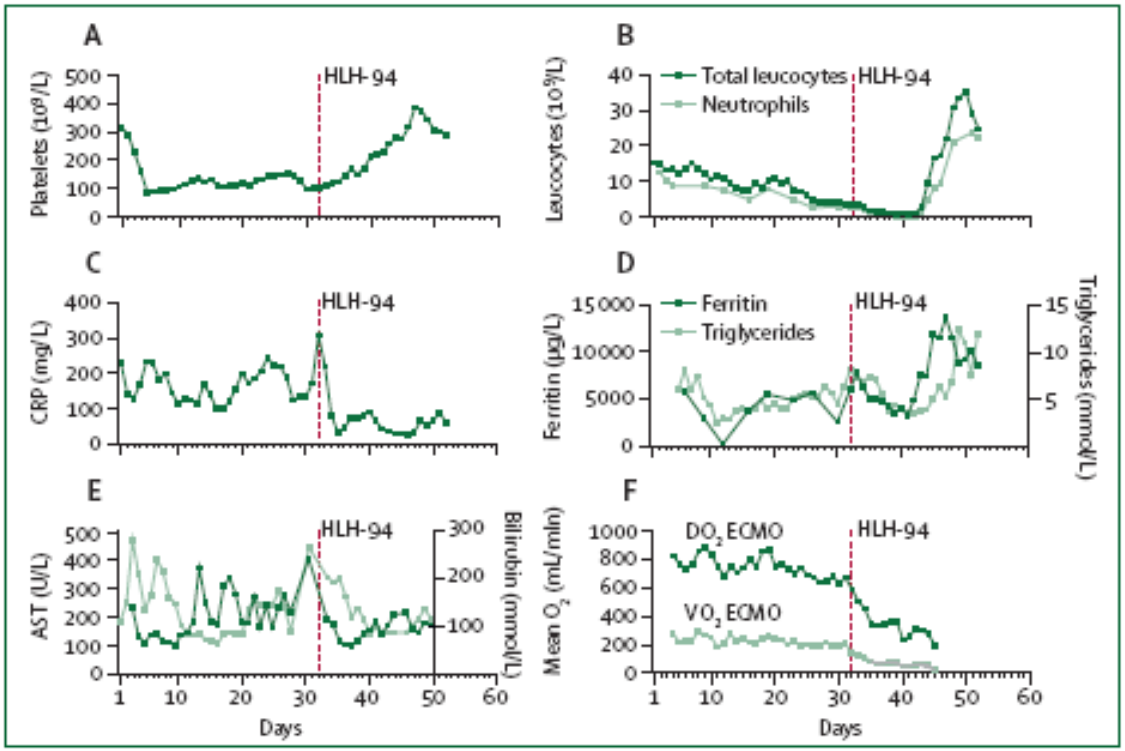
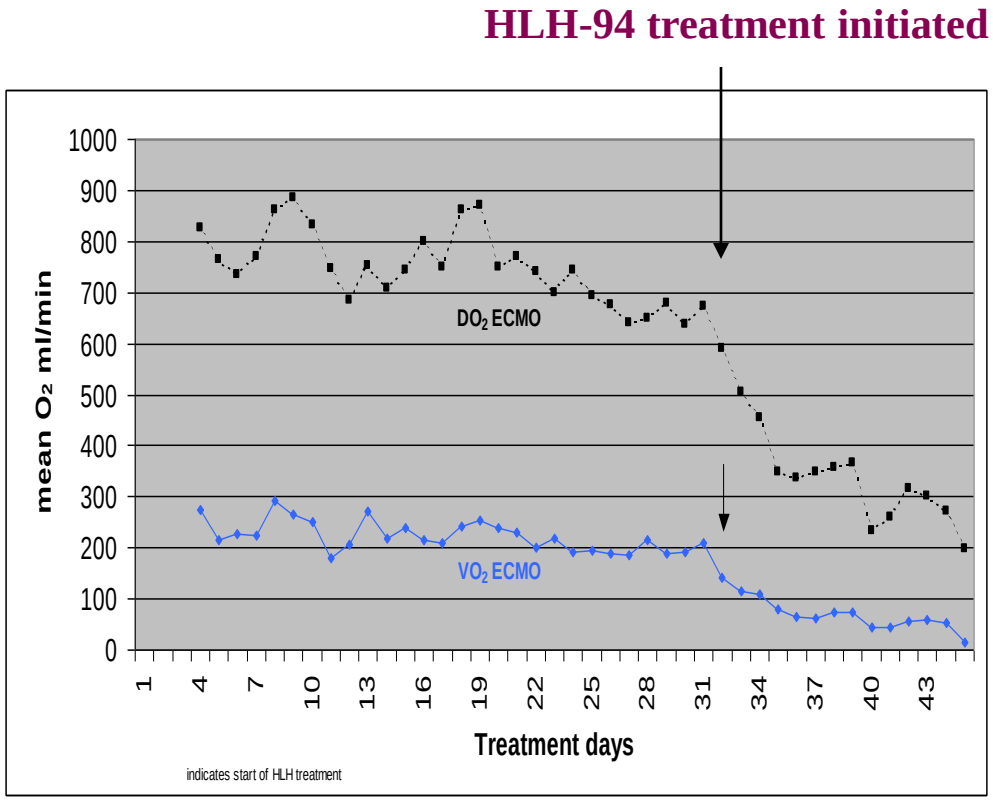


Figure: **Laboratory values and pulmonary function prior to and after initiating HLH therapy**
Etoposide 75 mg/m² was administered on day 32, and betamethasone from day 32. (A) Platelet counts. (B) Leucocyte and neutrophil counts (G-CSF initiated day 41). (C) CRP. (D) Serum ferritin and plasma triglycerides levels. (E) Serum aspartate aminotransferase (AST) (dark green) and bilirubin levels (light green). (F) Oxygen consumption (VO_2) and oxygen delivery (DO_2) during ECMO, calculated from pre- (venous) and post-oxygenator (arterial) blood samples. As the pulmonary function improved, oxygen delivery by ECMO could be reduced.

Cytotoxic therapy for severe swine flu A/H1N1



Oxygen consumption (VO2) and oxygen delivery (DO2) during ECMO, calculated from pre-(venous) and post-oxygenator (arterial) blood samples.

As the pulmonary function improves, from the first day of HLH therapy, oxygen delivery by ECMO could be reduced.

Henter JI, et al, Lancet 2010; 376: 2116

Expensive?

- No !!!

- Etoposide 100 mg/m^2 = 150 mg per adult
- Cost of 150 mg = 30-40 USD (per week)

- Total cost = only 60-80 USD per patient

Added Value of Research in Rare Diseases

1. For patients with Rare Diseases (RD) - and their families
2. + For individuals with other, related diseases
3. + For individuals with other, non-related diseases
4. = For the Society as a whole

Rare Diseases -

Challenges and Solutions

Dreams – on patients with Rare Diseases

- A well structured way to make the diagnosis
  → What is wrong? Which is my disease?
- A validated treatment to cure or reduce complications
  → How can health care help? How can we measure the effect?
- Trustable information on patient outcome
  → What will life be like?
- Understanding - from psychosocial issues to the disease biology
  → Why did it happen?
- Easily available information on the disease for physicians and patients

Clinical Studies – Can fulfill these dreams

- A well structured way to make the diagnosis
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Clinical Science - Identify new potential drugs

1. Elevated levels of Interferon gamma in HLH
   → Henter JI, et al, Blood 1991;78:2918-22.

2. CD8+ T cells and Interferon gamma are essential for HLH
   → Jordan MB, et al. Blood 2004;104:735-43.

3. Neutralization of IFN-gamma defeats hemophagocytosis in mice
   → Pachlopnik Schmid J, et al. EMBO Mol Med 2009;1:112-124.

4. Can anti-Interferon-gamma be used in patients with HLH?
   → Ongoing collaborative effort with academia + pharma industry

Clinical Science - Essential in Rare Diseases

Clinical Science can:

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Some thoughts on the future

A. How to **organize** medical Meetings on Rare Diseases?

B. How to **integrate** Clinical Science and ICORD?

A. How to organize medical Meetings on Rare Diseases?

- One possibility (in my experience):

  → Scientific Meetings – arranged by the patient organizations

  - Win-Win – for all – Annual Meetings for more than 20 years
  - Allows interested scientists to meet, despite a rare disease
  - Allows patients' organisations access to recent scientific advances

B. How to integrate Clinical Science and ICORD?

- We have established an international forum, with
  - → Patient group representatives
  - → Industry representatives
  - → Society representatives

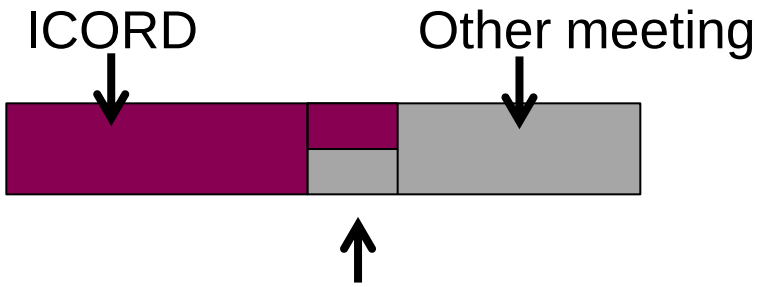
  - → However, clinical researchers are too few
    - They are the ones caring for the patients
    - They can improve diagnostics, therapy and care

Make ICORD a Large Rare Disease Forum?

- Family organisations arrange Scientific Society Annual Meetings at ICORD?
  - →Access to physicians, new therapy and research
  - →Support research and academic clinical trials

  - →One common day for all Societies
    - Statistical lectures
    - Clinical trials support, ethical applications, FDA/COMP

Possibility: Back-to-back to other meetings?



One day with common topics, for both meetings:

- Design of clinical trials
- Regulatory issues
- New drug development
- Patient group collaboration
- Meet with FDA, EMA, NIH
- Meet industry represent
- Learn from each other

Possibility: Back-to-back to <u>many</u> meetings?

One day with common topics:

- Design of clinical trials
- Regulatory issues
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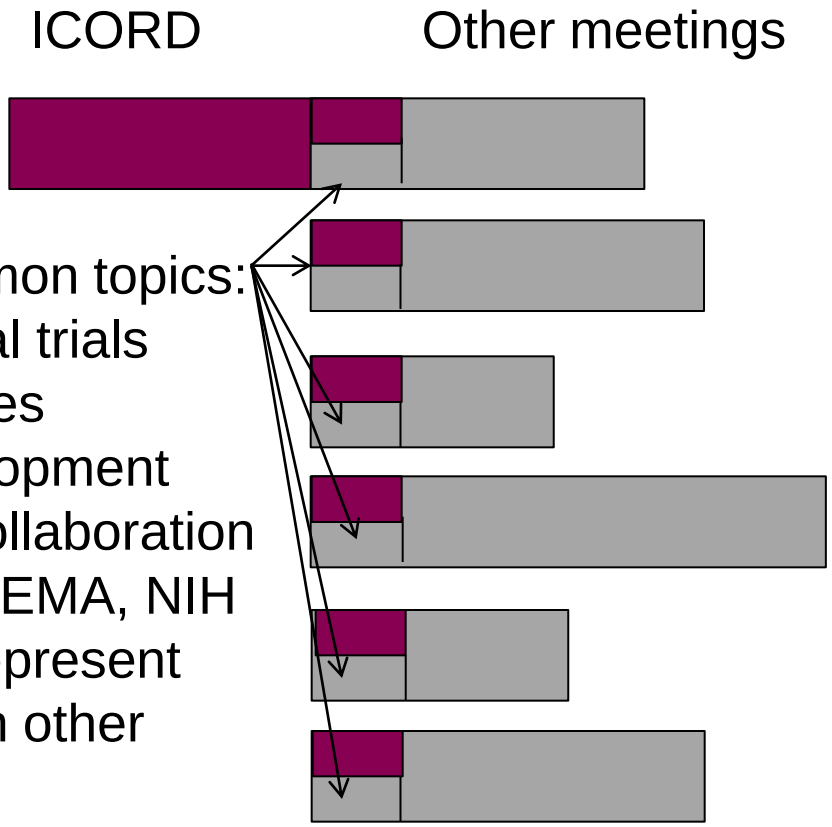

Conclusion

Successful Academic Clinical Trials in Rare Diseases can be Valuable also for Common Diseases

Thank you for your attention!