ECRIN
EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK

IA-Integrating Activity

Capacities – Research Infrastructures
FP7-INFRASTRUCTURES-2011-1.1.5
ECRIN-IA

Hitos del Ensayo Clínico

Xavier Carné

www.ecrin.org

CLÍNIC
BARCELONA
Hospital Universitari

International Clinical trials day 20 May, 2013, Madrid

SEVENTH FRAMEWORK PROGRAMME

International Clinical Trials' Day

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- since 2005 ECRIN hosts ICTD in one European capital
- Promote public awareness of the challenges raised by clinical research
- Stimulate debates between representatives of European patients associations, clinical scientists, scientific agencies, sponsors, ethics committees, competent authorities, medical journal editors, citizens

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12 milestones in the history of Clinical Trials (I)

a personal account

- c 600 BCE: Daniel's controlled nutritional study. Reported in Old Testament
- c 400 BCE: Hippocratic Oath
- 1500s: Paracelsus (von Hohenheim) "..by our own observation, confirmed by… experiment by reasoning thereon"
- 1747: James Lind first clinical trial
- c 1890: DV Dmitriev. First informed consent form for a volunteer donating part of his thyroid gland for transplantation and 1900: Walter Reed. Written consent form in English and Spanish
- 1902: Albert Moll's book. Medical Ethics. It recommends advisory boards to consider ethical aspects of human experiments

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12 milestones in the history of Clinical Trials (II)

a personal account

- 1923: R.A. Fisher & W.A. Mackenzie; Statistical randomization in an agricultural experiment
- 1931: J.B. Amberson et al; Publish negative results of a placebo controlled RCT on sanocrysin (gold) in the treatment of tuberculosis
- 1937: Sir Austin Bradford Hill; recommends randomization in his book “Principles of Medical Statistics”
- 1946: BMRC begins placebo controlled RCT of whooping cough vaccination (published in 1951)
- 2005: ICMJE requires registration of clinical trials prior to publication; and WHO specifies 20 minimal registration data set
- 2005: ECRIN is born……

Ref: Goldfarb N: Milestones in Clinical Research. J Clin Res Best Pract 2006

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International Clinical Trials' Day
20th May

celebrates the 20 May 1747 when James Lind started his famous trial of 12 scurvy-ridden sailors

1716-1794

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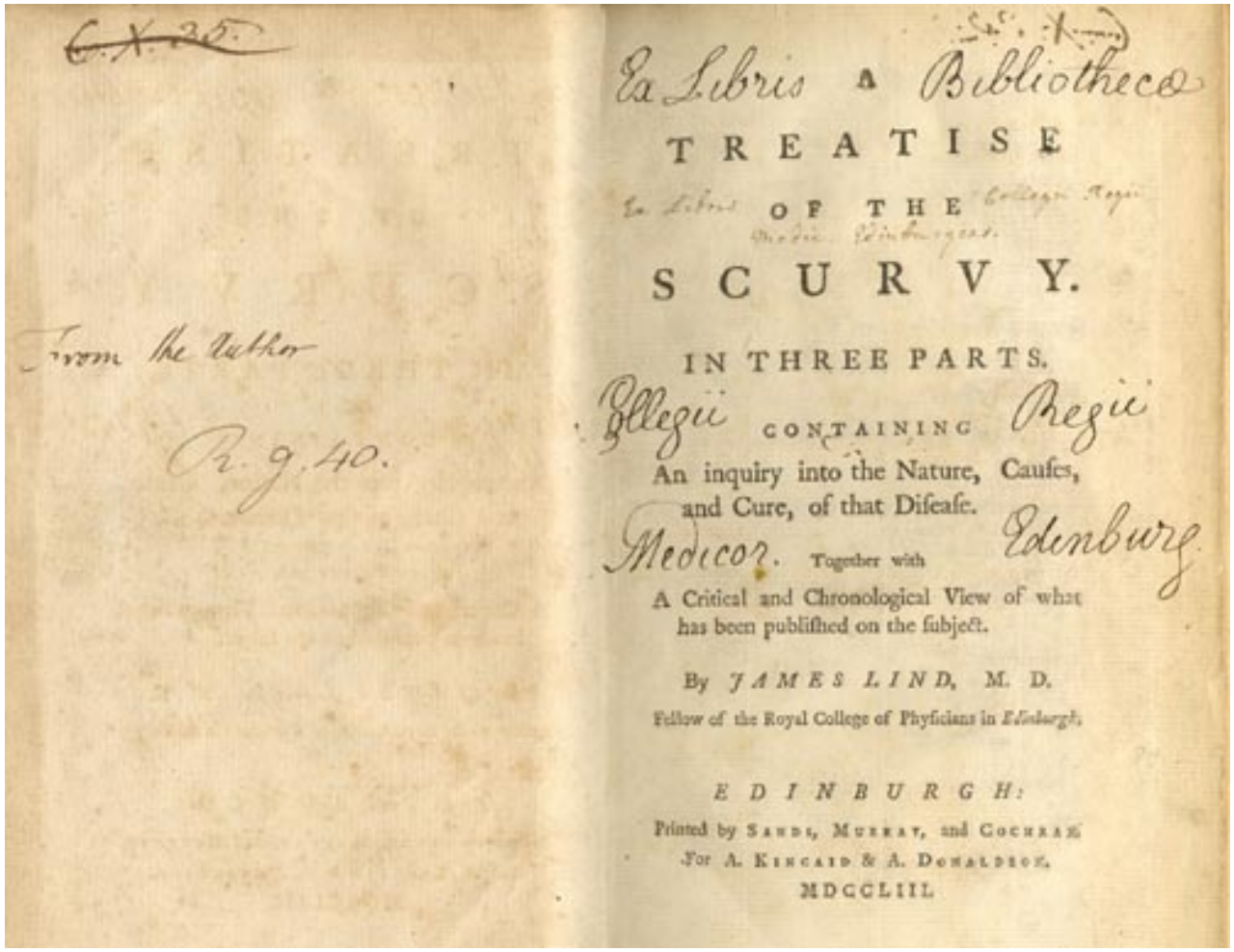
James Lind *(Edinburgh, 1716-1794)*



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From the Author

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Ex Libris A Bibliotheca

TREATISE

Ex Libris OF THE

SCURVY.

IN THREE PARTS.

Collegii CONTAINING Regii

An inquiry into the Nature, Cauſes,
and Cure, of that Diſeaſe.

Medicor. Together with Edinburg.

A Critical and Chronological View of what
has been publiſhed on the ſubject.

By JAMES LIND, M. D.

Fellow of the Royal College of Phyſicians in *Edinburgh*.

EDINBURGH:

Printed by SANDS, MURRAY, and COCHRAN.

For A. KINCAID & A. DONALDSON.

MDCCLIII.

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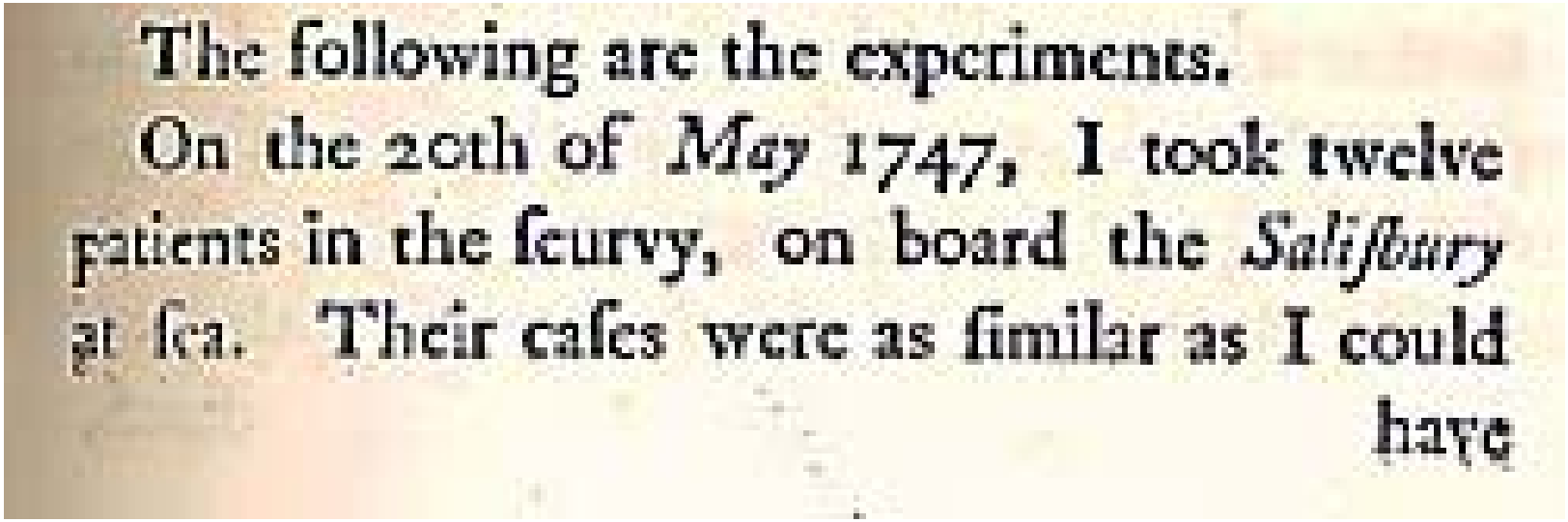
James Lind's trial



The following are the experiments.

On the 20th of *May* 1747, I took twelve patients in the scurvy, on board the *Salisbury* at sea. Their cases were as similar as I could have

2 got oranges and lemons
2 got cider
2 got vinegar
2 got elixir vitriol
2 got a concoction of spices, garlic, and mustard seeds
2 got sea water

Within six days, the 2 sailors given oranges and lemons became well

ECRIN

Integrating clinical research in Europe

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EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK

About ECRIN | Support / Tools | News | Contact

Home

Welcome to the European Clinical Research Infrastructures Network

The European Clinical Research Infrastructures Network (ECRIN) is a sustainable, not-for-profit infrastructure supporting multinational clinical research projects in Europe.

Latest News

Proposal for an EU Regulation on Clinical Trials

A joint statement from non-commercial and commercial organisations

We welc...
read more

The celebration of the 2012 International Clinical Trials Day in Spain

May 22-25, 2012

The celebration of the 2012 International Clinical Trials ...
read more

ESFRI Roadmap Research infrastructures
Biological and Medical Sciences

2006

BBMRI - Biobanks

EATRIS - Translational research facilities

ECRIN - Clinical trial platform

ELIXIR – Data repositories

Infrafrontier - Mouse archives and clinics

INSTRUCT - Structural biology facilities

EMBRC - Marine biology resources

2008

ERINHA - High-security labs

EuroBioImaging – Imaging facilities

EU-Openscreen - Chemical libraries

ANAE - Analysis and experimentation on ecosystems

2010

ISBE – Infrastructure for systems biology

MIRRI – Microbial resources

BBMRI
Biobanking and Biomolecular Resources Research Infrastructure

EATRIS

ECRIN

ELIXIR

Infrafrontier

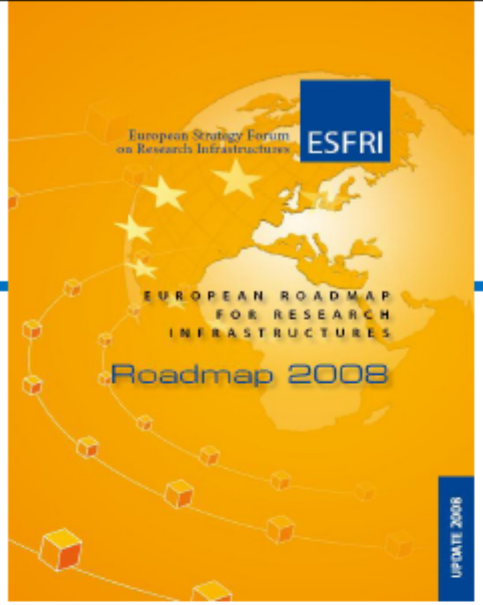
INSTRUCT

EMBRC
EUROPEAN MARINE BIOLOGICAL RESOURCE CENTRE

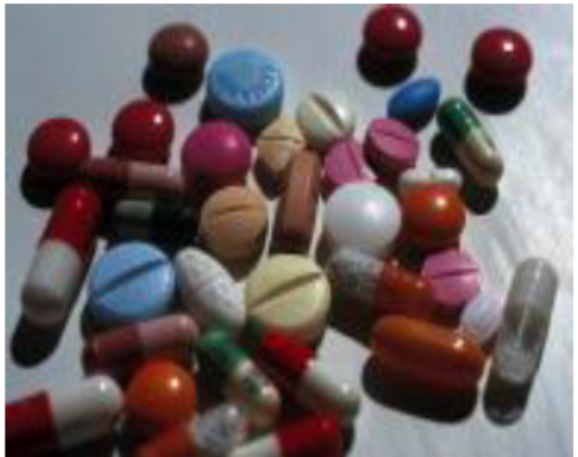
erinha

EURO-BIOIMAGING

EU-OPENSCREEN
ESFRI ROADMAP 2008



A pan-European infrastructure for clinical research in any disease area



Make Europe a single area for clinical research

Pan-European, distributed infrastructure providing coordinated services to ***multinational*** clinical research in Europe:

- access to ***patients*** and to ***expertise*** throughout Europe

- despite the ***fragmentation*** of health, legislative and funding systems

- ***support*** to investigators and sponsors in multinational studies

ECRIN development steps

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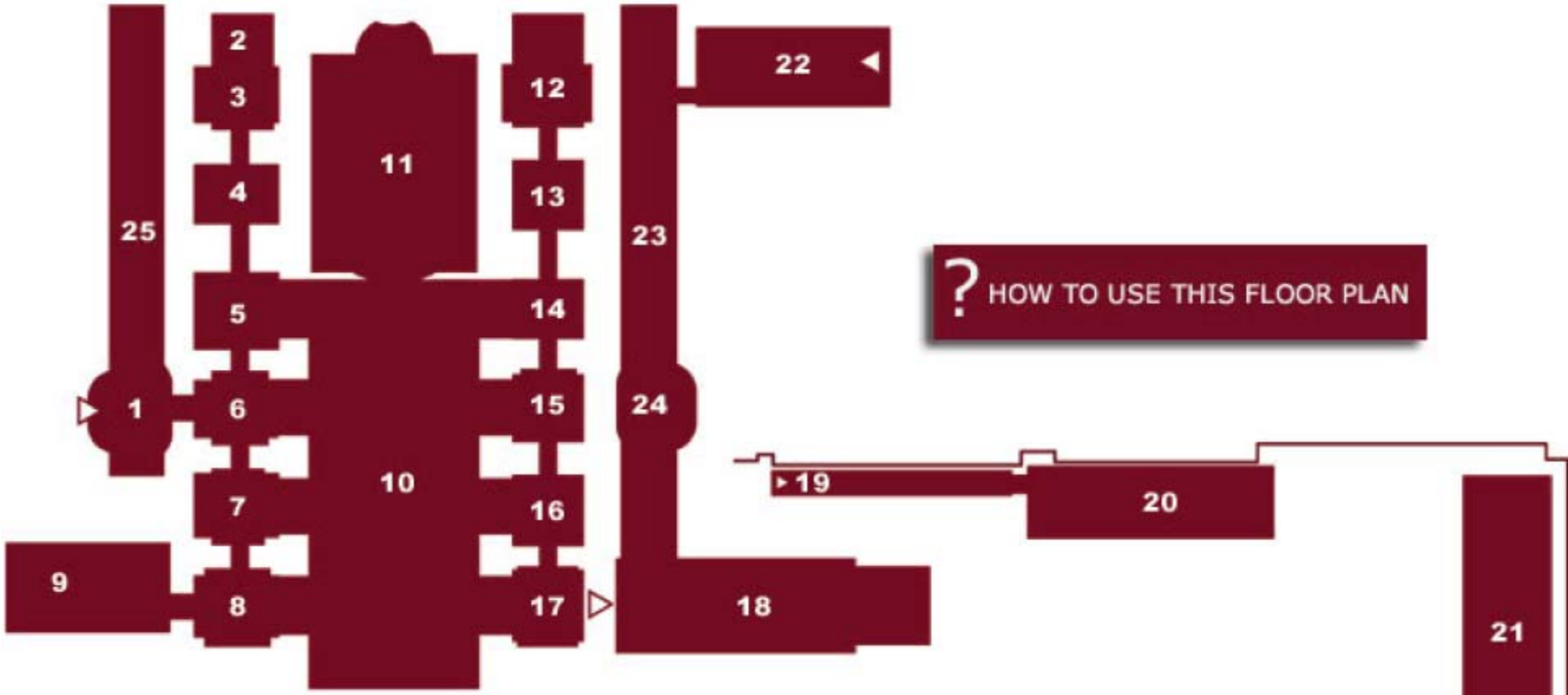
	ECRIN-RKP (2004-2005) identifying bottlenecks	
	ECRIN-TWG (2006-2008) developing know-how	
	ECRIN-PPI (2008-2011), building the infrastructure and supporting pilot multinational trials	
	ECRIN-ERIC (2013->) operating the ESFRI-roadmap infrastructure for multinational trials	
	ECRIN-Integrating Activity (2012->16) Expanding connections	


Barre des Ecrins
French Alps
alt. 4102 m
ECRIN-ERIC
OPERATIONS
ECRIN-IA
STRUCTURING
ECRIN-PPI
ECRIN-TWG
ECRIN-RKP
ECRIN

What is a distributed infrastructure ?



List of Chapels

The chapel of the Langue of Castille, Leon and Portugal
The chapel of the Langue of Provence
The chapel of the Langue of Aragon
The chapel of the Langue of Auvergne
The chapel of Our Lady of Philermos
The chapel of the Langue of Italy
The chapel of the Langue of Germany
The chapel of the Langue of France
The chapel of the Anglo-Bavarian Langue

ECRIN-IA (2012-15)

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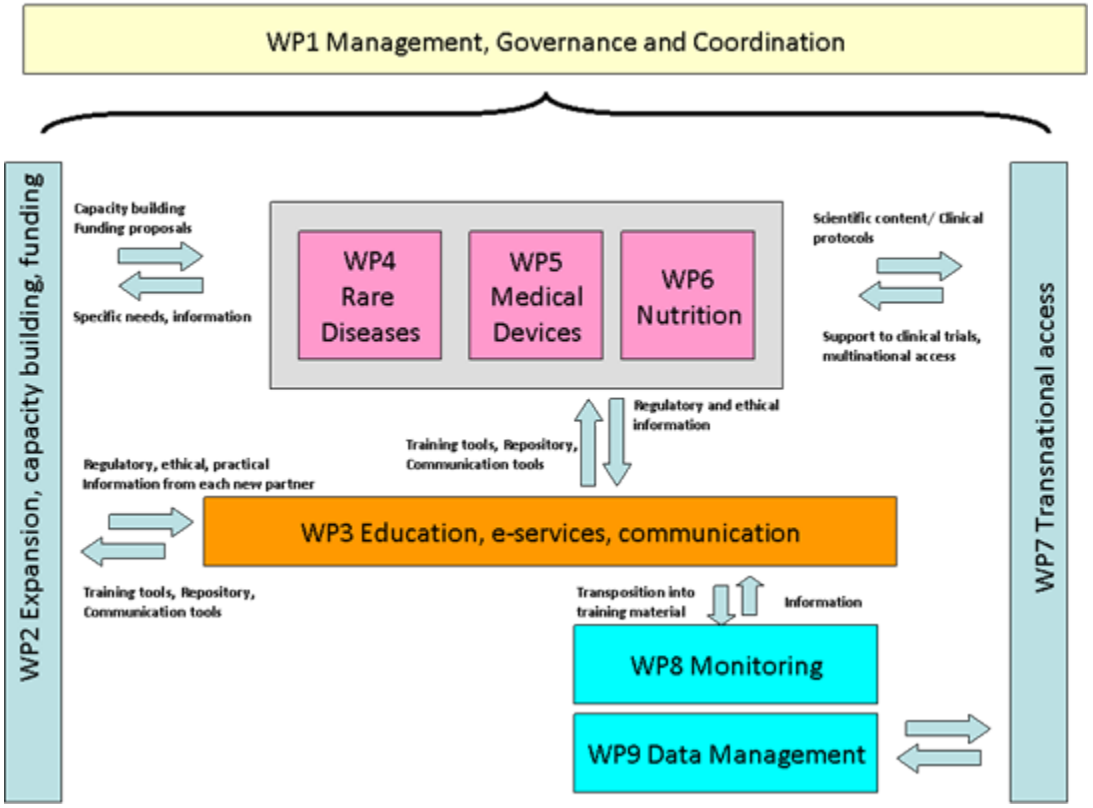

(i) *Networking activities,* to foster a culture of co-operation between research infrastructures and scientific communities and help developing a more efficient and attractive European Research Area;

(ii) *Trans-national access and/or service activities,* to support scientific communities in their access to the identified research infrastructures;

(iii) *Joint research activities*, to improve, in quality and/or quantity, the services provided by the infrastructures.

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How does ECRIN support multinational trials ?

➢ **Information and consultancy during the preparation of the trial**

- Information on regulatory and ethical requirements
- Information on sites and participant recruitment
- Information on clinical trials units
- Information on insurance
- Information on cost and funding opportunities
- Information on contracting
- Adaptation to local context

Full protocol

Scientific evaluation

Logistical assessment

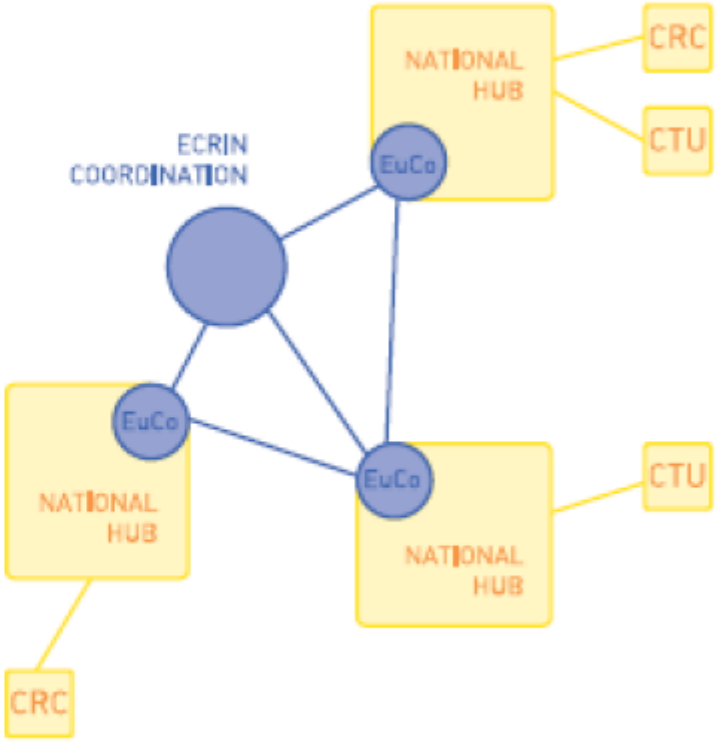
Contract with sponsor

➢ **Services during the conduct of the trial**

- Interaction with competent authorities and ethics committees
- Support with insurance contracting
- Adverse event reporting
- Monitoring
- Data management
- Investigational medicinal product management
- etc.

Network of European Correspondents

- Single contact point
- Hosted in national hubs
- Local relay in ECRIN activities
  - structuring
    - developing common tools and know-how
  - operations
    - providing information and consulting
    - coordinating the support and services



Access to ECRIN

- **Based on the full protocol**
- **Scientific Board**
  - Silvio Garattini, Chair (pharmacology)
  - Christian Gluud (hepatology and methodology)
  - Xavier Carné (clinical pharmacology)
  - *Jordi Llinares (rare disease)*
  - *Athanasios Pallis (cancer)*
  - *Michael Boehm (cardiovascular)*
  - *Miguel Viana Baptista (neurology)*
- **External peer-reviewers (3)**

- **Logistical assessment by the EuCos**

Scientific Board: Acceptance criteria

1 - Multicentre trial run in at least two European countries.

2 - Rules for transparency:

- Commitment to register the trial in a public register before inclusion of the first participant, for example on www.clinicaltrials.gov.
- Commitment to publish results irrespective of findings.
- Commitment to make raw anonymised data sets available to the scientific community upon legitimate request to the sponsor or principal investigator once the trial is completed.
- Declaration of conflicts of interest.

3 - Rationale based on up-to-date systematic reviews of clinical data or, where not possible, of preclinical data on the experimental intervention and comparator.

4 - Clinical relevance and/or marked impact on public health.

5 - Suitable overall trial design appropriate to the clinical question, including for example:

- Selection of an appropriate and justified experimental intervention and comparator.
- Adequate sample size with supporting calculation.
- Relevant patient population (inclusion and exclusion criteria), setting, and duration of treatment and follow up.
- Outcome measures for efficacy and safety with clinically meaningful benefit for the patient.

Scientific Board: Recommendations

1 - Randomized superiority design is preferable for efficacy assessment, rather than non-inferiority.

2 - Use of the best available comparator.

3 - Primary outcome measure most suitable for patient and public health's interests.

4 - Sample size calculation based on the primary outcome measure, and power calculation for other important outcome measures.

5 - Adequate recording of adverse events.

6 - Adequate strategies to reduce or control possible biases, for example central randomisation; blinding of all parties (at least assessors, statisticians); intention-to-treat analysis for efficacy in superiority trial; blinded conclusions drawn before breaking the allocation code; and interpretation of, and decision to publish results, independent of funding source.

7 - Description of potential risks and how to handle them, including involvement of and charter for independent data monitoring and safety committee.

8 - Description of governance structure of the project including responsibility for coordination, data analysis, and independent monitoring.

9 - Description of indications of feasibility, for example: committed clinical sites; expected participant recruitment to meet sample size; resources and funding available; and logistics of delivering the intervention(s).

10 - Involvement of pertinent patient organisation (if available) in the protocol design.

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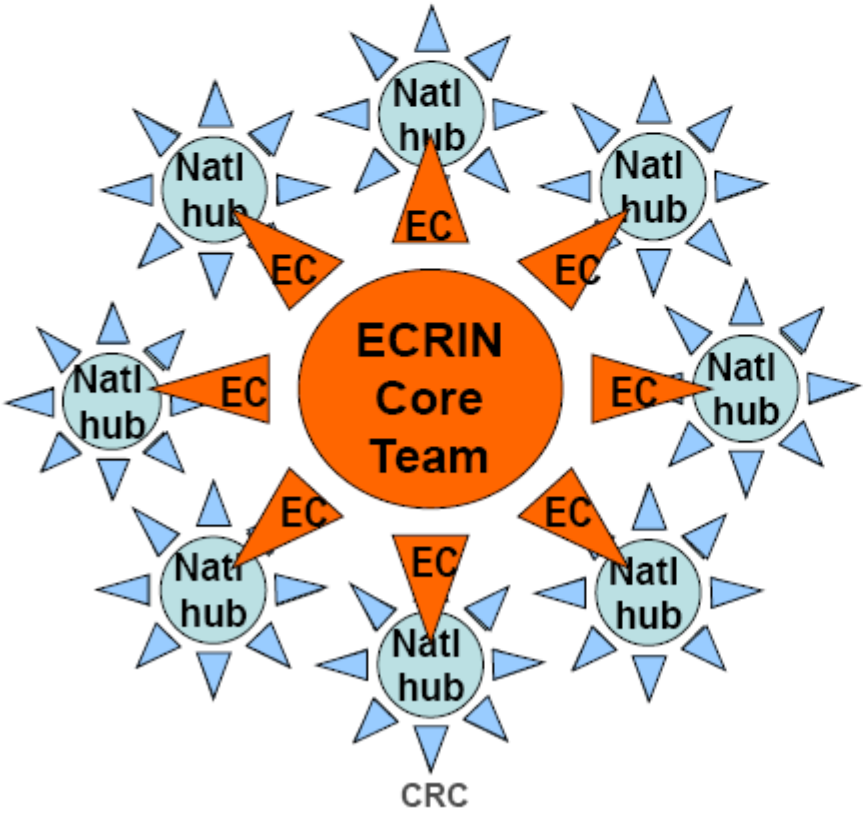
ECRIN-ERIC objective/ mission

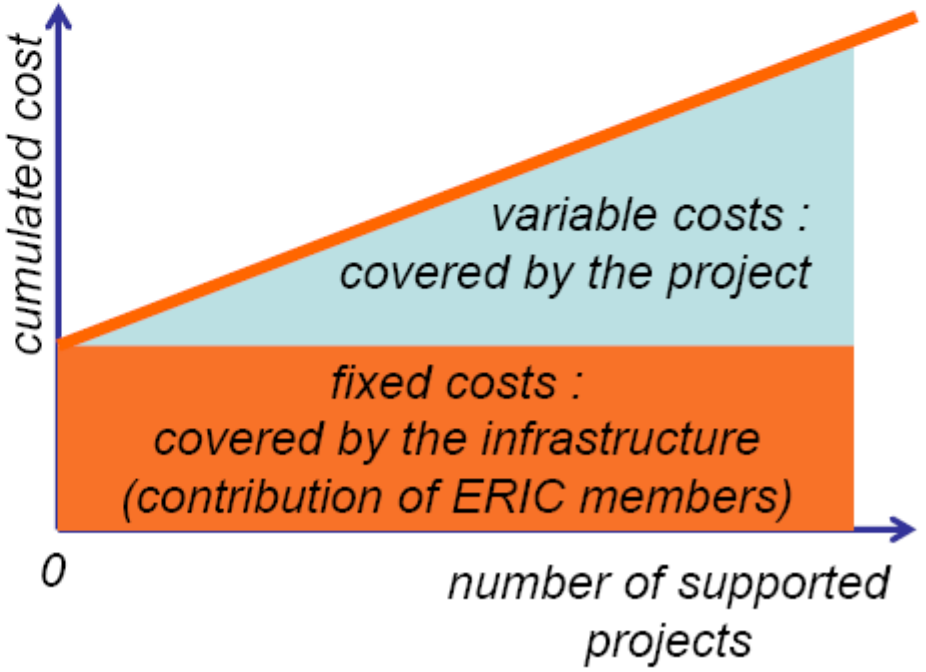
- ECRIN-ERIC is designed to provide a sustainable not-for-profit distributed platform for the support to pan-European clinical research projects in any medical field and for any category of research
  - operate the infrastructure
  - provides consultation, advices and services through a network of academic organisations specialized in clinical research

ECRIN-ERIC business model

For non-economic activities
- plus limited economic activities (max 10-20%)

Infrastructure -> fixed costs
Project -> variable costs





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ECRIN-ERIC

MEMBER COUNTRIES

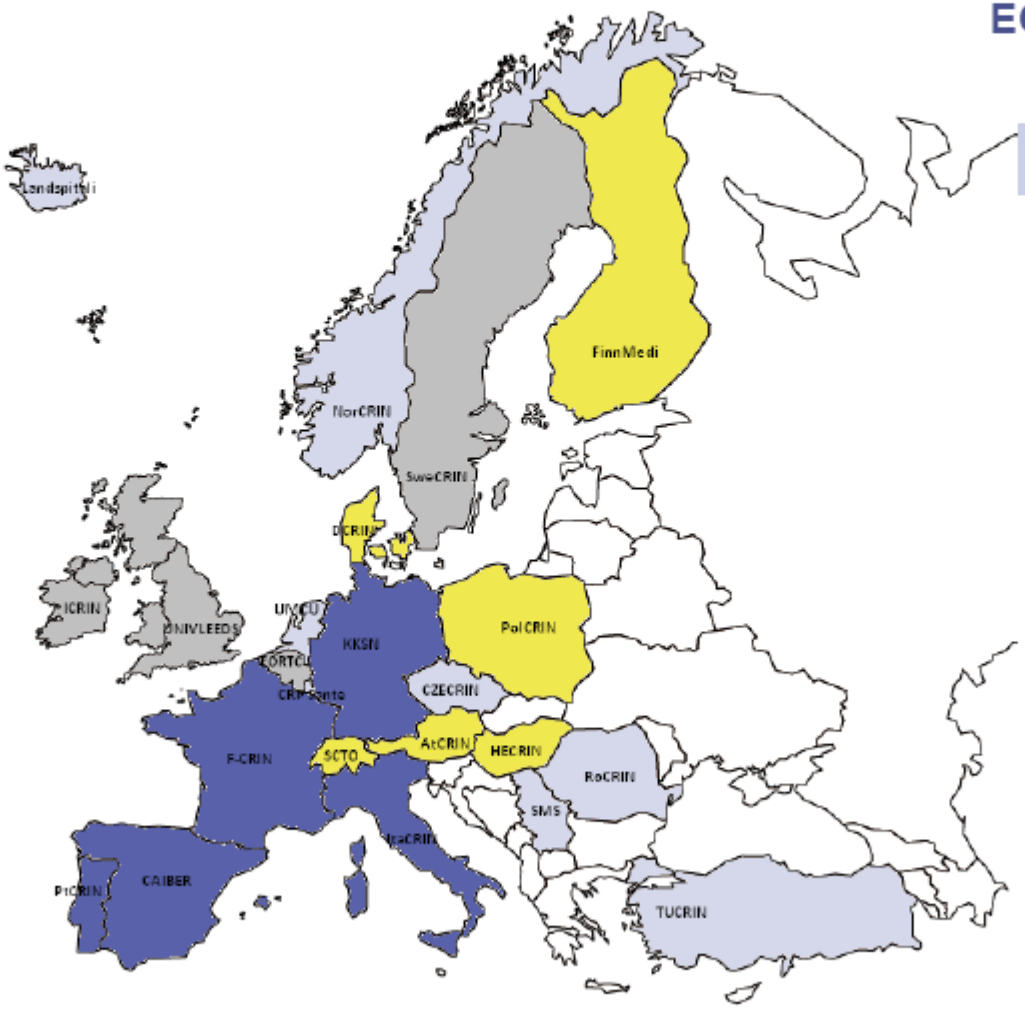
FRANCE
GERMANY
ITALY
PORTUGAL
SPAIN

SCIENTIFIC PARTNERS NON MEMBERS

Austria - MUW (for AtCRIN)
Denmark - RH (for DCRIN)
Finland- Finn-Medi
Hungary - HECRIN
Poland - MUW PL (for PolCRIN)
Switzerland – SCTO

AFFILIATE PARTNERS

EU - EORTC
Ireland - MMI (for ICRIN)
Sweden - KI (for SweCRIN)
UK - UNIVLEEDS



ECRIN-IA PROJECT PARTNERS

NEW COUNTRIES

Czech Republic - MU
Iceland - Landspitali
Luxemburg - CRP Santé
Norway - ST OLAVS
Romania - UMFCV
Serbia - SMS
The Netherlands - UMCU
Turkey - DEU

INSTITUTIONS

CIRM- Italy
ESPEN - Belgium
Eurordis- France
FCRB- Spain
INRA- France
IRFMN- Italy
Qualissima- France
UDUS- Germany
UniTransferKlinik- Germany
VSOP- The Netherlands

Clinical trials supported

IA-Integrating Activity

Trial	Phase	Number of Countries	Number of patients	Status
Scandinavian Starch for Severe Sepsis/Septic Shock Trial	III	5	804	Completed
TTM-trial (Target Temperature Management after Cardiac Arrest)	III	12	850	Recruiting
Phase I intranasal genetically modified *B. pertussis*	I	2	48	Completed
PRE clinical mutation CARriers from families with DIlated cardiomyopathy and ACE inhibitors	III	7 (7 sites)	200	Recruiting
Efficacy and safety of anti-Pseudomonas (IgY) in cystic fibrosis	III	5 (18 sites)	180	Recruiting
Fluconazole versus Micafungin in neonates with Candidiasis	II/III	5	100	Preparation phase

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Trial	Phase	Number of countries	Number of patients	Status
Transfusion Requirements In Septic Shock trial	III	5 (23 sites)	1000	recruiting
Safeguarding the Brain of Our Smallest Children	II	12	100	Recruiting (1 country) approval in 3 countries)
Ivermectin (different doses) for the treatment of Strongyloidiasis	III	5 (11 sites)	400	Not yet recruiting
Efficacy of FOLFOX alone, FOLFOX plus bevacizumab and FOLFOX plus panitumumab as perioperative treatment in patients with resectable liver metastases from wild type KRAS colorectal cancer	II	10	360	Not yet recruiting

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis

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Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D.,
Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D.,
Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D.,
Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D.,
Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D.,
Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D.,
Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D.,
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Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D.,
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Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D.,
for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

ABSTRACT

BACKGROUND

Hydroxyethyl starch (HES) 130/0.4 is widely used for fluid resuscitation in intensive care units (ICUs), but its safety and efficacy have not been established in patients with severe sepsis.

The authors' affi
Appendix. Addre
Dr. Perner at the
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- The scientist's task:

To imagine & gather data that can convince yourself (& the community) that your hitherto accepted theories are wrong

¡Muchas gracias

Nos vemos en

Mayo de 2014¡