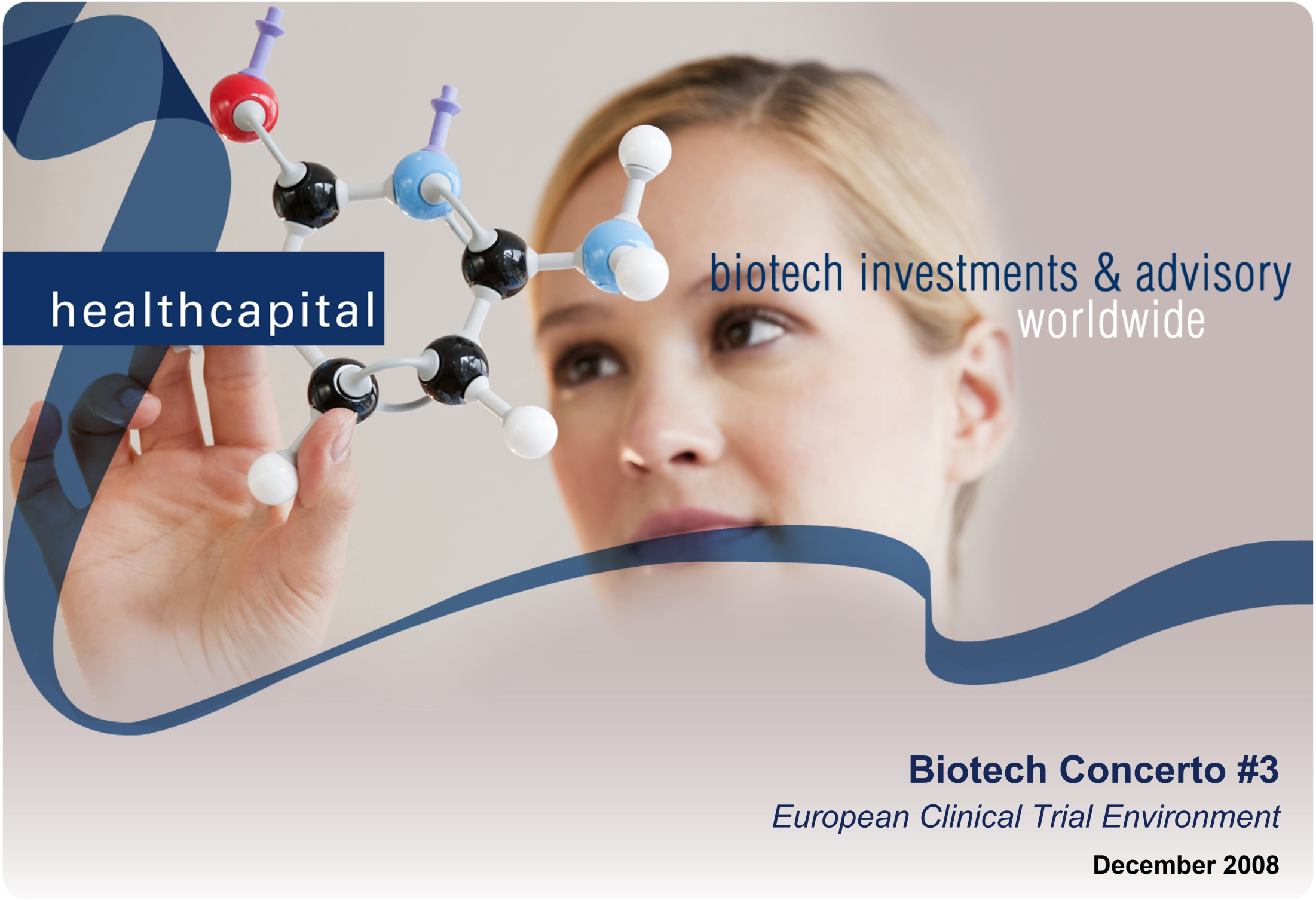

Biotech Concerto #3

European Clinical Trial Environment

December 2008

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EU Directive 2001/20/EC

OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001

on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

Source: Francis P. Crawley, Good Clinical Practice Alliance

EU Approval System (as of May 1, 2004)

- 27 national approaches with a common minimal basis
  - defined in Directives and Guidelines
  - but implemented in national law, ordinances, decrees of costs, etc. at different times

- The approval remains a national issue, even if the application has been submitted in all European countries in parallel

Source: Hartmut Krafft, PEI, CTFG

European Authority: EMEA

The European Medicines Agency (EMEA) is a decentralized body of the European Union with headquarters in London. It is responsible for the scientific evaluation of applications for European marketing authorization for medicinal products (centralized procedure).

All medicinal products for human and animal use derived from biotechnology and other high technology processes must be approved via the centralized procedure. The same applies to all human medicines intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases.

The safety of medicines is monitored constantly by the Agency through a pharmacovigilance network. The EMEA takes appropriate actions if adverse drug reaction reports suggest changes to the benefit/ risk balance of a medicinal product.

Source: EMEA

IRB and Ethics Committee

Institutional Review Boards (IRBs) are also known as an independent ethics committee or ethical review board.

The Ethics Committee, according to Directive 2001/20/EC, is an independent body in a Member State of the European Union, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and well being of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the clinical trial protocol, the suitability of the investigators involved in the trial and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

With the Clinical Trials Directive, the European Union (EU) envisioned a harmonization of research ethics committees (RECs) across Europe, including the time taken to assess a trial proposal and the kinds of issues a committee should take into account.

Source: Wikipedia

The Guidance Documents

- Detailed Guidelines on the principles of good clinical practice in the conduct in the EU of clinical trials on medicinal products for human use
- Detailed guidance on the application format and documentation to be submitted inan application for an ethics committee opinion on a clinical trial on a medicinalproduct for human use
- Detailed guidance for the request for authorization of a clinical trial on a medicinalproduct for human use to the competent authorities in the European Union, notification of substantial amendments and declaration of the end of a clinical trial
- Detailed guidelines on the trial master file and archiving to implement the directive on Clinical Trials on medicinal products for human use
- Detailed guidance on the collection, verification and presentation of adversereaction reports arising from clinical trials on medicinal products for human use
- Detailed guidance on the European database of Suspected Unexpected SeriousAdverse Reactions (Eudravigilance-Clinical Trial Module)
- Detailed guidance on the European clinical trials database (EUDRACT Database)
- Detailed guidelines on inspection procedures for the verification of GCP compliance to implement the directive on Clinical Trials on medicinal products for human use

Source: Francis P. Crawley, Good Clinical Practice Alliance

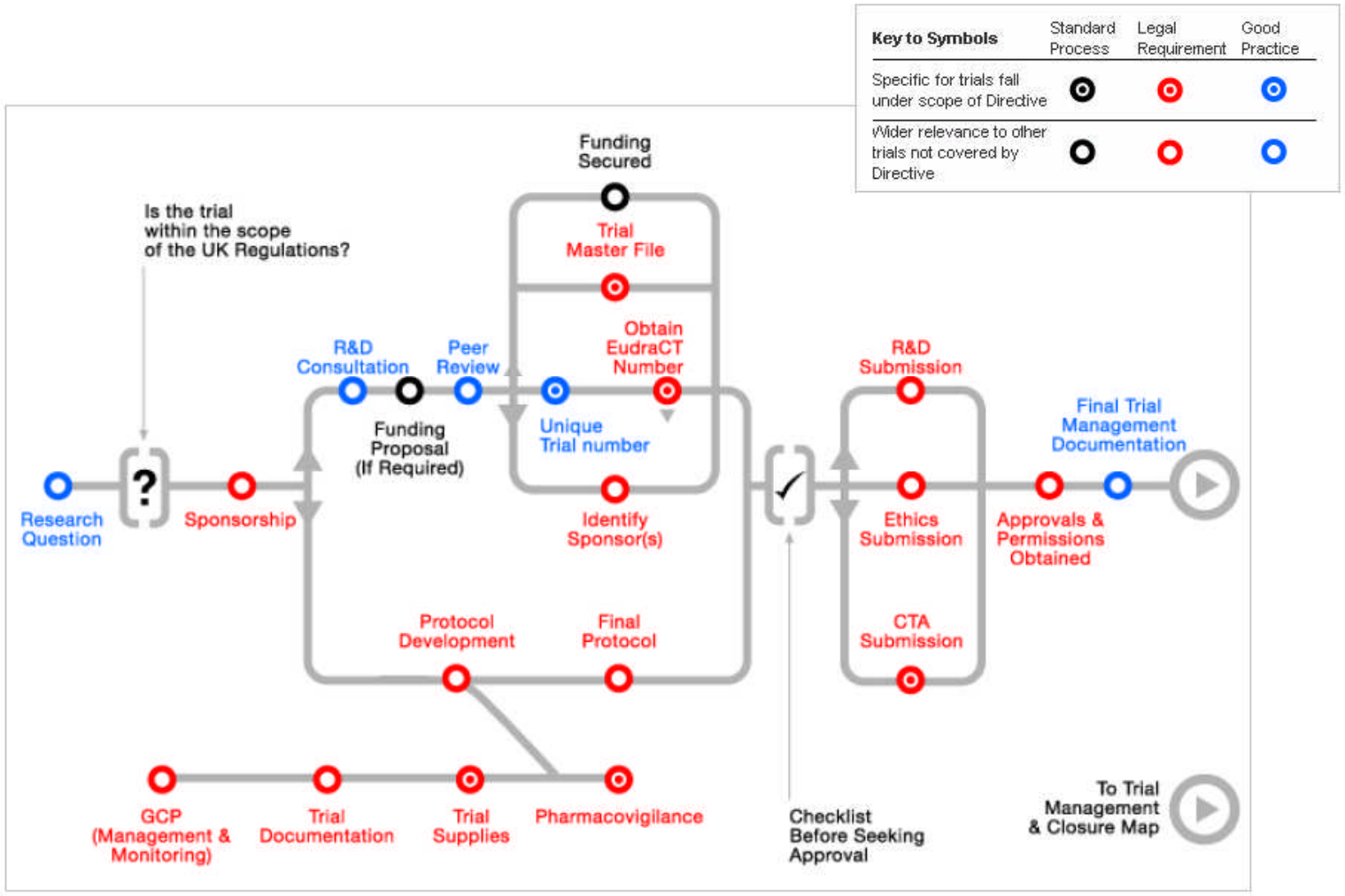
The Guidance Documents (cont.)

- Detailed guidelines on the qualifications of inspectors who should verify compliancein clinical trials with the provisions of Good Clinical Practice for an investigational medicinal product to implement the directive on Clinical Trials on medicinal products for human use
- Manufacturing and/or Import Authorization of Investigational Products for Human Use-Contents of the Application
- Authorization Referred to in Article 13, Paragraph 1 of Directive 2001/20/EC: Requirements to Obtain Authorization and Requirements to Be Met by the Holder of This Authorization
- Draft Proposal for a Commission Directive…/…/EC Amending 91/356/EEC, Laying Down the Principles and Guidelines of Good Manufacturing Practice for Medicinal Products for Human Use
- Modifications of Commission Directive 91/356/EEC of 13 June 1991 Laying Down the Principles and Guidelines of Good Manufacturing Practice for Medicinal Products for Human Use (*two column informal working document)*
- Volume 4: Good Manufacturing Practices; Annex 13: Manufacture of Investigational Medicinal Products; November 2001

Source: Francis P. Crawley, Good Clinical Practice Alliance

Route Map (UK Example)

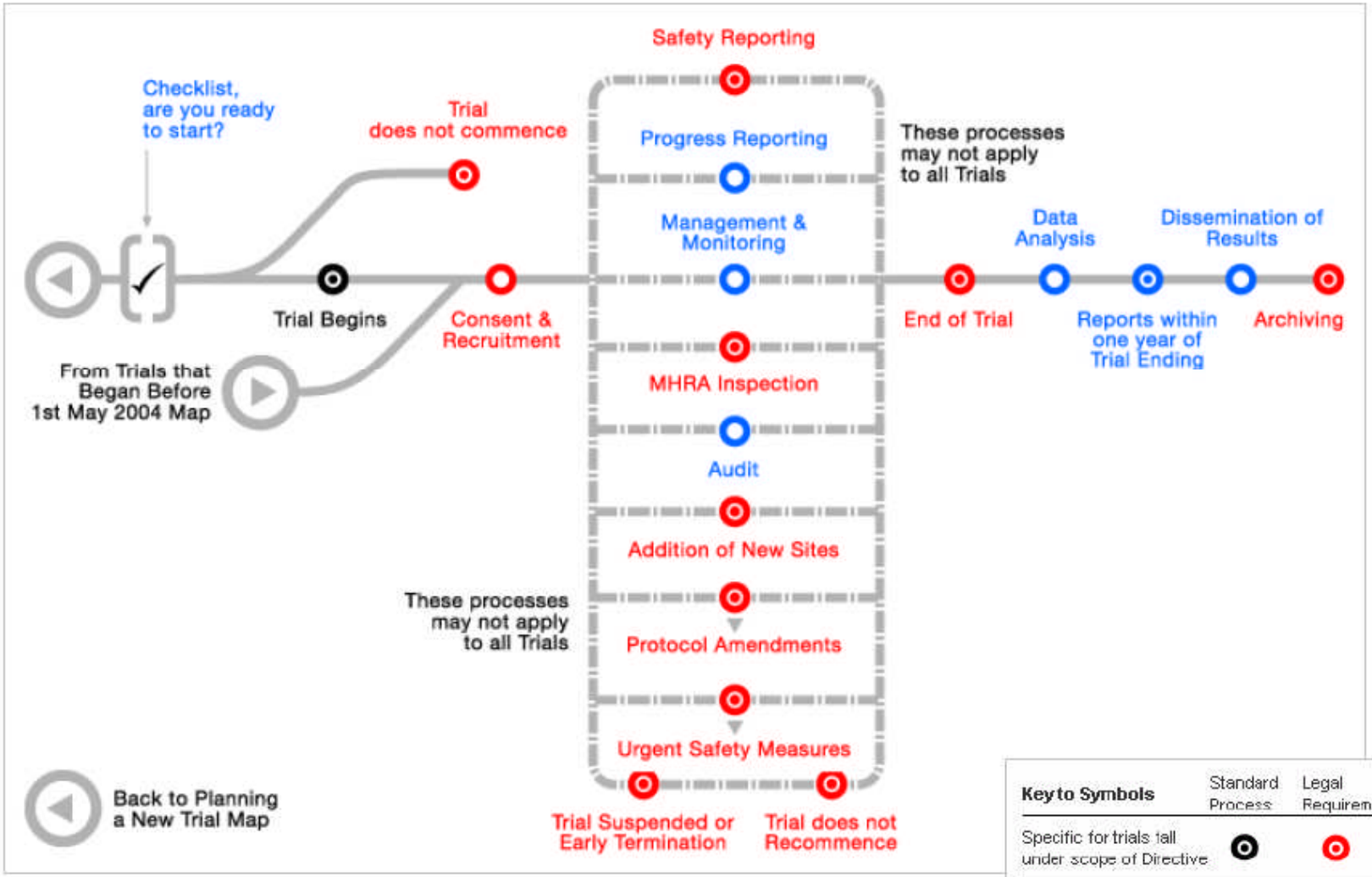
Planning a New Clinical Trial



Source: www.ct-toolkit.ac.uk, adapted

Route Map (UK Example)

Trial Management and Closure



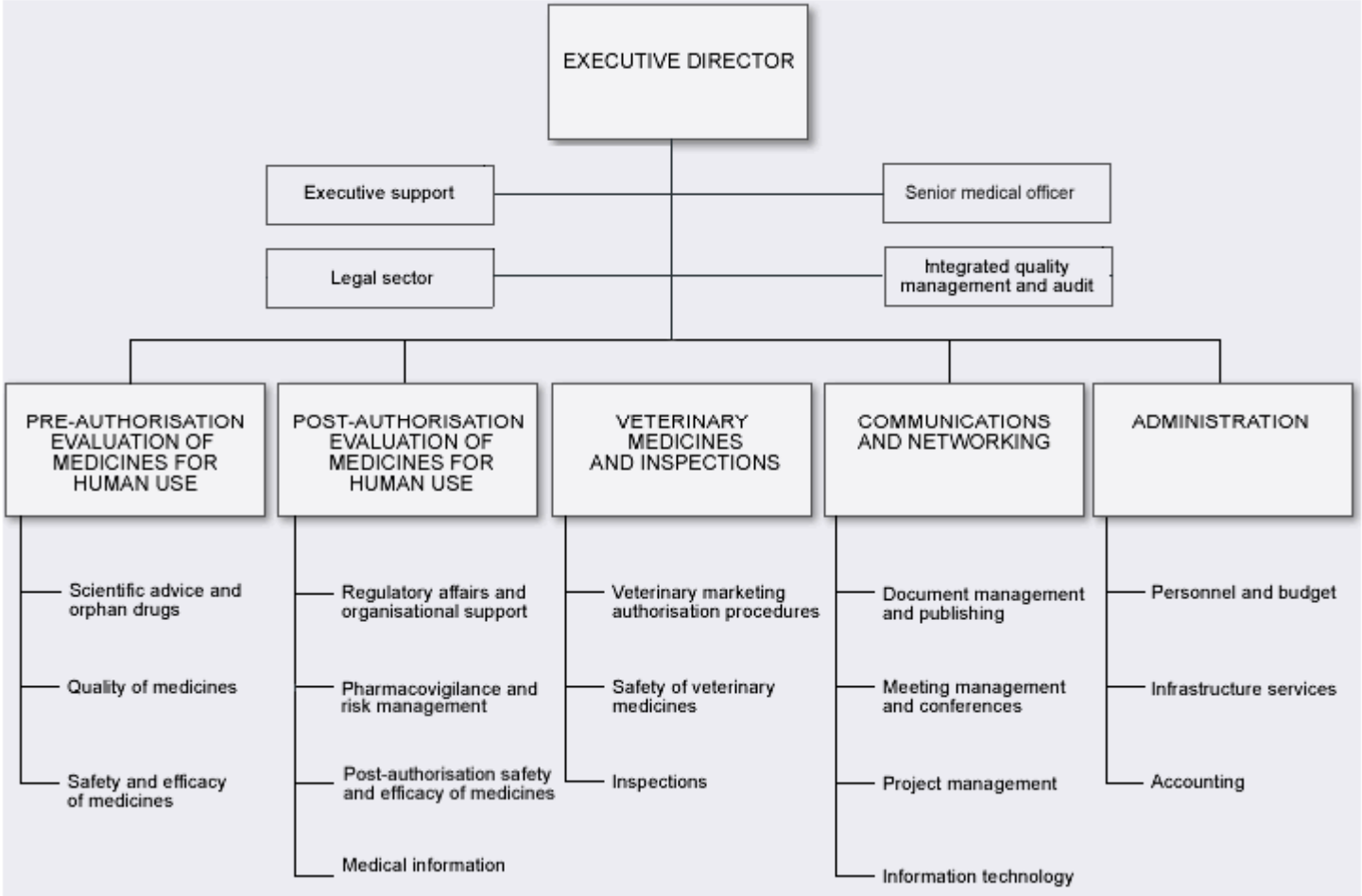
Source: www.ct-toolkit.ac.uk, adapted

Challenges

- Lack of consistency across member states regarding the contents of the ‘Clinical Trials Application’ (CTA)
- Lack of a consistent definition of an ‘Investigational Medicinal Product (IMP)’
- Lack of clarity and consistency regarding the definition of ‘substantial amendment’
- Lack of consistent GMP requirements for IMPs across member states
- No mutual recognition procedures between competent authorities
- Inconsistent application formats to ethics committees within and across Member States
- Inconsistent ethical review approaches
- Need for a simplification and harmonization of EU legislation in pharmaceuticals
- Definition of ‘non-interventional’ clinical trials needs clarification
- SUSAR definition unclear
- Eudravigilance Database not being used or resourced consistently and effectively
- Recommitment to the implementation of the Directive in a harmonized manner

Source: Francis P. Crawley, Good Clinical Practice Alliance

EMEA Organization Chart



Source: EMEA

Stakeholders*

- Francis P. Crawley, Executive Director, Good Clinical Practice Alliance (GCPA) Europe
- Prof. Hartmut Krafft, Chairman of the Clinical Trial Facilitation Group (CTFG)
- Georgette Lalis, Director, DG Enterprise and Industry, European Commission
- Thomas Lönngren, Executive Director EMEA
- Fernand Sauer, Director of the Directorate Public Health and Risk Assessment,
- Health & Consumer Protection Directorate General, European Commission

* alphabetical order by last name

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