EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Polish Academy of Science - Warsaw 19 May 2017
Medical, Ethical and Legal Aspects of Experimental therapy

Experimental therapy: the EMA perspective

Presented by Marisa Papaluca Amati
Senior Scientific Advisor – Scientific Committees Regulatory Strategy
European Medicines Agency

Experimental therapies: ethics and regulatory science

EUROPEAN MEDICINES AGENCY

Ethics principles
core to the public health mandate of Regulatory Agencies

- manufacturing authorisations
- animal testing facilities authorisation/3Rs
- scientific advice on tests and trials
- clinical trials evaluation, approval, monitoring
- marketing authorisation applications evaluation including GCP inspections
- beyond initial regulatory approval

Good Clinical Practices

international ethical and scientific standards for designing, conducting, recording and reporting

trials that involve the participation of human subjects

1. Rights, safety and well-being of trial subjects protected, consistent with the principles of the Declaration of Helsinki

2. Clinical trial data obtained is reliable and useful to make safe effective medicines available to all in need

Data protection

Transparency

Autonomy **Non-maleficence** **Beneficence** **Distributive justice**

Goals

- Subjects/patients participating in trials are fully protected – wherever the trial takes place should comply with GCP, with a robust scientific rationale and with a relevant design

- Processes in the conduct of the study and data generated are of high quality and useful *to monitor each patients' response* and adequate for *peer review* and *regulatory decision making*

- Availability of safe and effective new medicines

- *Regulatory pathways* including Priority Medicines, Medicines Access to Patients, Art 58, Compassionate use

Directorate-General for Health & Consumers

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 March 2012
EMA/CHMP/BWP/534898/2008
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

Draft Agreed by Biologic Working Party	January 2010
Adoption by Committee for Medicinal Products for Human Use for release for consultation	18 February 2010
Start of public consultation	28 February 2010
End of consultation (deadline for comments)	31 August 2010
Agreed by Biologic Working Party	7 March 2012
Adoption by Committee for Medicinal Products for Human Use	15 March 2012
Date for coming into effect	15 April 2012

Keywords	***Biological product, investigational medicinal product (IMP), clinical trial, quality***

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

Table of contents

Experimental therapies: ethics and regulatory science

EUROPEAN MEDICINES AGENCY

Regulatory science assessment

Quality and manufacturing, safety, efficacy, information, risk minimisation measures

The type of the medicine (e.g. biotech/orphan/ ATMP)

The *proven* scientific rationale
Design of studies and trials
for reliable and robust clinical data

Benefit/risk balance

Ethical assessment

The ethical assessment focuses on the evaluation of the ethics of the clinical development programme.

Non-compliance with ethical principles may indicate more widespread problems with impact on

benefit-risk assessment.

Experimental therapies: ethics and regulatory science

EUROPEAN MEDICINES AGENCY

Clinical trials Authorisations

- National Competent Authorities (NCAs) in Member States are responsible for the regulatory aspects and Ethics Committees (EC) for the ethical ones
- Each EC has its own operational framework, while views on ethical matters vary among EC members and different ECs but all address:
  - risk-benefit balance
  - vulnerable participants
  - informed consent process
  - advertising for recruitment of participants
  - investigators' qualifications
  - conflicts of interest
  - tissue/blood sampling
  - Post-trial access to treatment
- NCAs ensure that ECs have reviewed the Ethical aspects before authorising the trial

Autonomy

Marketing authorisation applications

Compliance with Good Clinical Practices rules a must for validation of trials intended for decision making

- Informed consent
- Vulnerable participants and special populations
- Clinical trials in third countries
- Placebo vs comparator
- Applicability of data to EEA population

- Trials population shall be representative of exposure in clinical care: elderly, children, ethnic variants, women
- Particular weight is carried out by GCP violations

Non-maleficence

GCP inspections

- GCP inspections identify issues related to the ethical aspects of the design, conduct and reporting of clinical trials and/or to the reliability of the data collected during a clinical trial.
- Pre-authorisation GCP inspections in the context of the Centralised Procedure are a tool to support the evaluation process for marketing authorisation.

Beneficence

Post-approval

- Clinical exposure in studies after conditional or exceptional circumstances marketing authorisation
- Pharmacovigilance systems
- Pharmacovigilance inspections
- Post-approval efficacy and safety studies
- Risk management plans
- Signals detection
- Registries and real world data
- Protection from falsified information and products
- Distribution chains oversight
- Availability of medicines

Distributive justice

Experimental therapies: ethics and regulatory science

EUROPEAN MEDICINES AGENCY

ETHICS

Common ethical pitfalls related GCP inspection findings

1. Informed consent process (especially in vulnerable populations),

2. Subject safety, protocol non-compliance (related to inclusion, exclusion or withdrawal criteria)

3. Lack of approval or late approval of a clinical trials (amendments) by the Ethics Committee, qualification of investigators/site staff, dosing aspects in clinical trials on healthy volunteers etc.

Experimental therapies: ethics and regulatory science

EUROPEAN MEDICINES AGENCY

- Medical research involving a disadvantaged or *vulnerable population or community is only justified if* the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research
- Every medical research study involving human subjects must be preceded by careful assessment of *predictable risks and burdens to the individuals* and communities involved in the research in comparison with foreseeable *benefits to them and to other individuals or communities* affected by the condition under investigation.

Points to consider on GCP inspection findings and the benefit-risk balance

Paper prepared by the GCP IWG and adopted by CHMP

- Ethical related GCP inspection findings – even if not directly influencing the benefit-risk balance - are important, as they raise serious questions about the rights, safety and well-being of trial subjects and hence the overall ethical conduct of the study.
- It is an obligation of clinical assessors, rapporteurs and the CHMP also to assess the ethics of a clinical development programme, and major ethical flaws should have an impact on the final conclusions about approvability of an application.
- Consequently, ethical misconduct could result in rejection of the application.
- Extensive non-compliance with ethical principles may indicate more widespread problems also affecting aspects of direct relevance to the benefit-risk assessment.

Useful documents in the public domain

Ethical considerations for clinical trials on medicinal products conducted with minors

Public consultation launched by the Commission between 1/06/2016-31/08/2016

With this public consultation the Directorate General for Health and Food Safety, DG SANTE, intends to seek the views of stakeholders – and other interested parties - on the document regarding "Risk proportionate approaches in clinical trials" which has been developed in preparation for *the implementation for the Clinical Trials Regulation (EU) No 536/2014*.

- The main objective of these recommendations is to provide further information on how a risk proportionate approach can be implemented in clinical trials and also highlights the areas identified in the clinical trials Regulation which support and facilitate such adaptations.
- https://ec.europa.eu/health/human-use/clinical-trials/developments_en
- Common recommendations on ethical aspects of clinical trials in minors will facilitate a harmonised approach to the application of the Clinical Trials Regulation across the EU, thereby facilitating the conduct of clinical trials in whichever country the trial occurs.
- In the ethical review, paediatric expertise is required to assess and balance the benefits, risks and burden of research with minors.
- Involvement of parents and children in the research development process is of importance, to be able to adequately address and incorporate their needs and preferences.
- The neonate represents a particularly vulnerable group of the paediatric age groups and requires even more careful trial review.

Useful documents in the public domain

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU / EEA and submitted in marketing authorisation applications to the EU regulatory authorities.

The aim of the paper is to strengthen existing processes to provide assurance to regulators and stakeholders that clinical trials meet the required ethical and GCP standards, no matter where in the world they have been conducted.

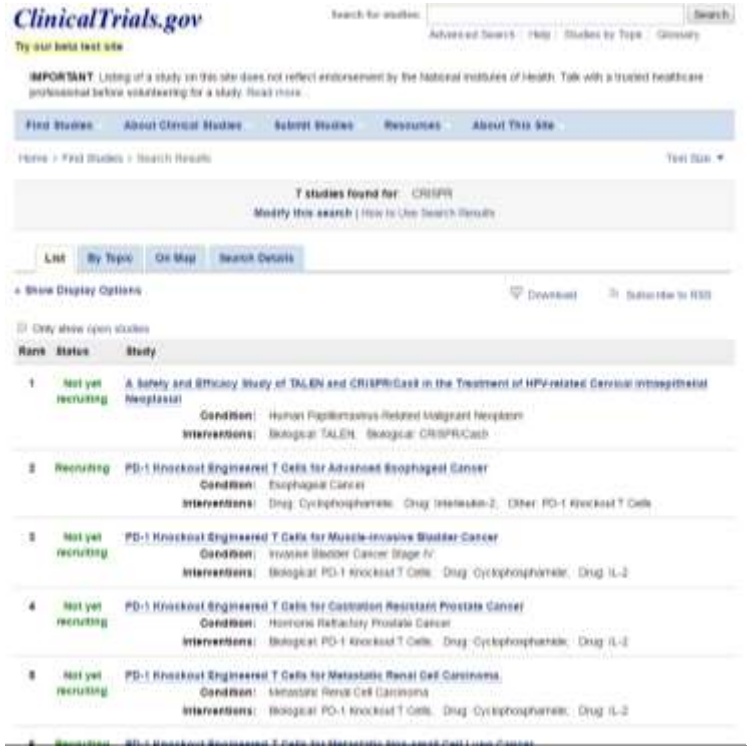
- Increasing globalisation of clinical research
- Concrete steps for international cooperation
- Practical steps by which EU regulators will gain assurance that ethical and GCP standards are applied to clinical trials for human medicines, both during the development and during the marketing-authorisation-application phase

Experimental therapies: ethics and regulatory science

EUROPEAN MEDICINES AGENCY

European Group on Ethics in Science and New Technologies (EGE)

Statement on Gene Editing https://doi.org/10.1515/jwiet-2017-0114



EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES

Statement
on
Gene Editing

In 1975 an international conference (the Asilomar Conference) was convened to consider the implications of the new technologies that were then becoming available to modify the genome of organisms through the insertion or deletion of segments of DNA. At that time it was only possible to genetically modify microorganisms. That conference instigated a moratorium on the genetic modification of humans – germline modification – and the interpretation of the discussions led to significant regulation of all forms of genetic 'manipulation', whether the organisms were modified and used in containment, or (later) when released into the environment.

The technology has changed very significantly over the last 40 years as we have learned to understand more of the processes by which genetic material is altered in microorganisms, plants and animals and it is now possible to precisely insert or delete sequences of DNA in situ. This forty year old global consensus on prohibiting human germline gene modification has come under significant pressure in 2015.

In February of this year, the UK parliament voted to approve regulations, following a rigorous debate, that permit the clinical use of mitochondrial replacement techniques. While mitochondrial gene transfer does not involve gene editing techniques, it could be argued that the approval of this limited form of germline gene modification did cross a Rubicon. There has been a rapid development in gene editing technologies in the last five years, and the announcement in April 2015 of genome editing of non-viable human embryos using CRISPR-Cas9 demonstrated that human germline gene modification has moved out of the realm of the theoretical, and clinical applications are becoming feasible. Techniques such as CRISPR-Cas9 can modify genomes of living organisms at *precise* locations in more *specific* ways and more *cost-effectively* than previously possible. This is already challenging the international regulatory landscape for the modification of human cells in the near to medium term.

Experimental therapies: ethics and regulatory science

EUROPEAN MEDICINES AGENCY

EDPS Workshop
On Data Driven Life
In cooperation with the EAG

festina lente

European Parliament
18 May 2017

It is a hallmark of the digital revolution we are experiencing that data infuses every aspect of society and private life. Our lives are being documented and even determined by the digital traces we leave behind and by the inferences organisations and algorithms make about that data. The massive collection of information allows private and public entities to predict our behaviour, score our reputation or nudge us to undertake certain actions. What are the positive and negative consequences of these data-driven changes for society as a whole and for our ability to pursue our own life choices?

AGENDA

8h15-9h00 Welcome, registration and coffee

9h00-9h30 Introductory speeches: Giovanni Buttarelli (EDPS) and Peter Burgess (EAG Chair)

9h30-10h30 Panel 1: Health and scientific research: epidemiology, genetics and rare diseases
Moderator: Giovanni Buttarelli

Speakers:
(1) speaker to be confirmed
(2) Dr. Effy Vayena, Professor of Health Policy, University of Zurich

10h30-11h00 Coffee break

11h00-12h00 Panel 2: Humanitarian intelligence: disaster response, risk management
Moderator: Peter Burgess

Speakers:
(1) Romain Bircher, Deputy Director of Communication and Information Management, CICR
(2) Prof. Dr. Andrej Zwitter, Political Science Department, University of Groningen

12h00-13h00 Panel 3: Money: finances, banking, insurances, credit scoring
Moderator: Aurélie Pols

Speakers:
(1) Elena Alfaro Martinez, Head of Data & Open Innovation BBVA
(2) Cecile Wendling, Head of Foresight, AXA

Patient paricipation: shift from «health for all» to «all for health»: meaning and ethical implications


EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES

Opinion
on the ethical implications of
new health technologies and citizen participation

Executive summary and Recommendations

1) Introduction and scope
2) Key ethical reflections
3) Recommendations

Europe to 2020: Together for health

Data intensive medicine

Increasing role of subjects in the production of data, knowledge and innovation.

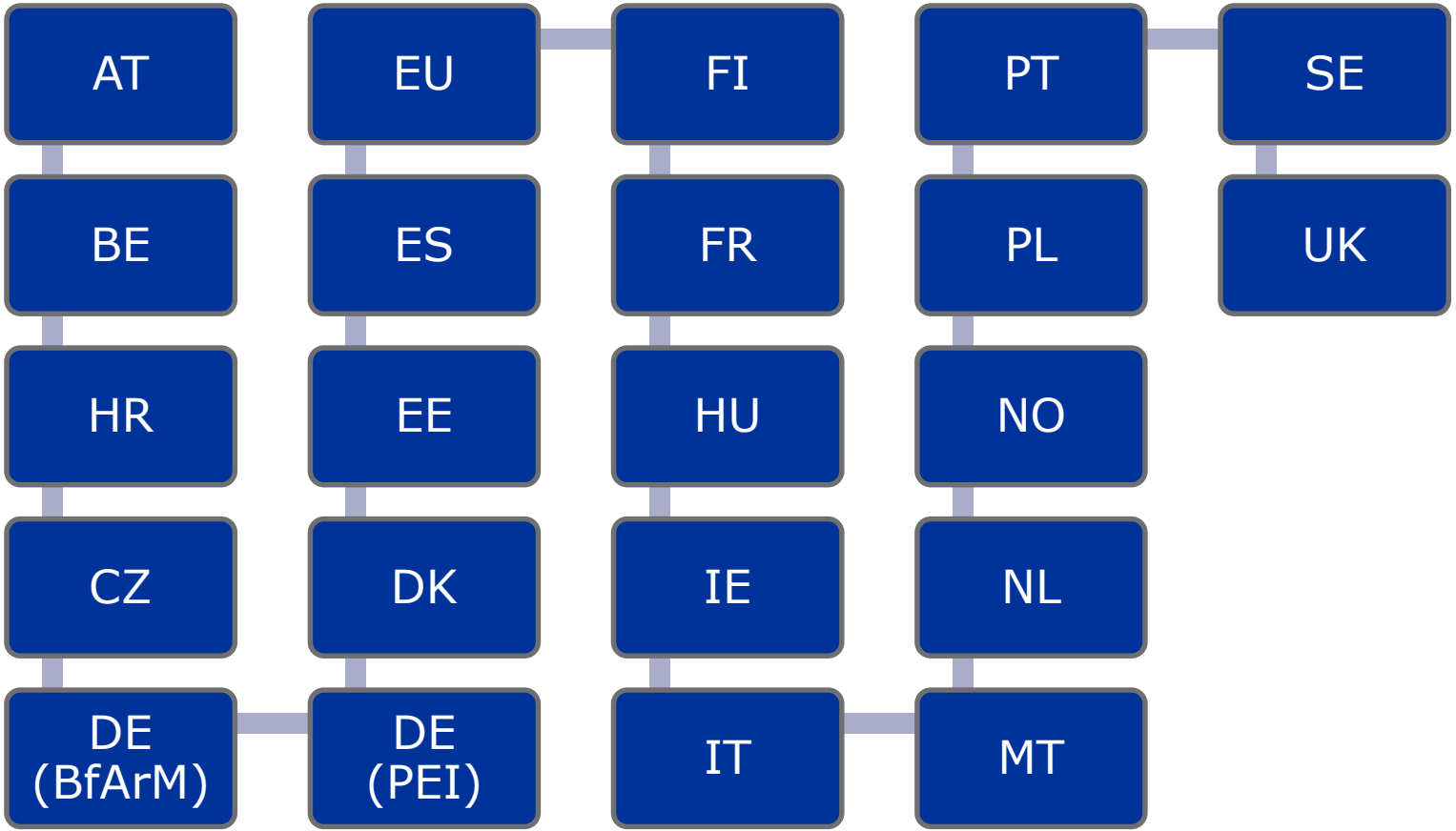
- New perception of the «self», of personhood and body
- Transformation of subject/physician relationship
- Subjects involvement in the research -> tensions between empowerment, engagement and exploitation
- Subjects involvement in societal understandings, principles and structures governing health
- Implications for notions of solidarity and justice

Joint HMA-EMA EU Innovation Network

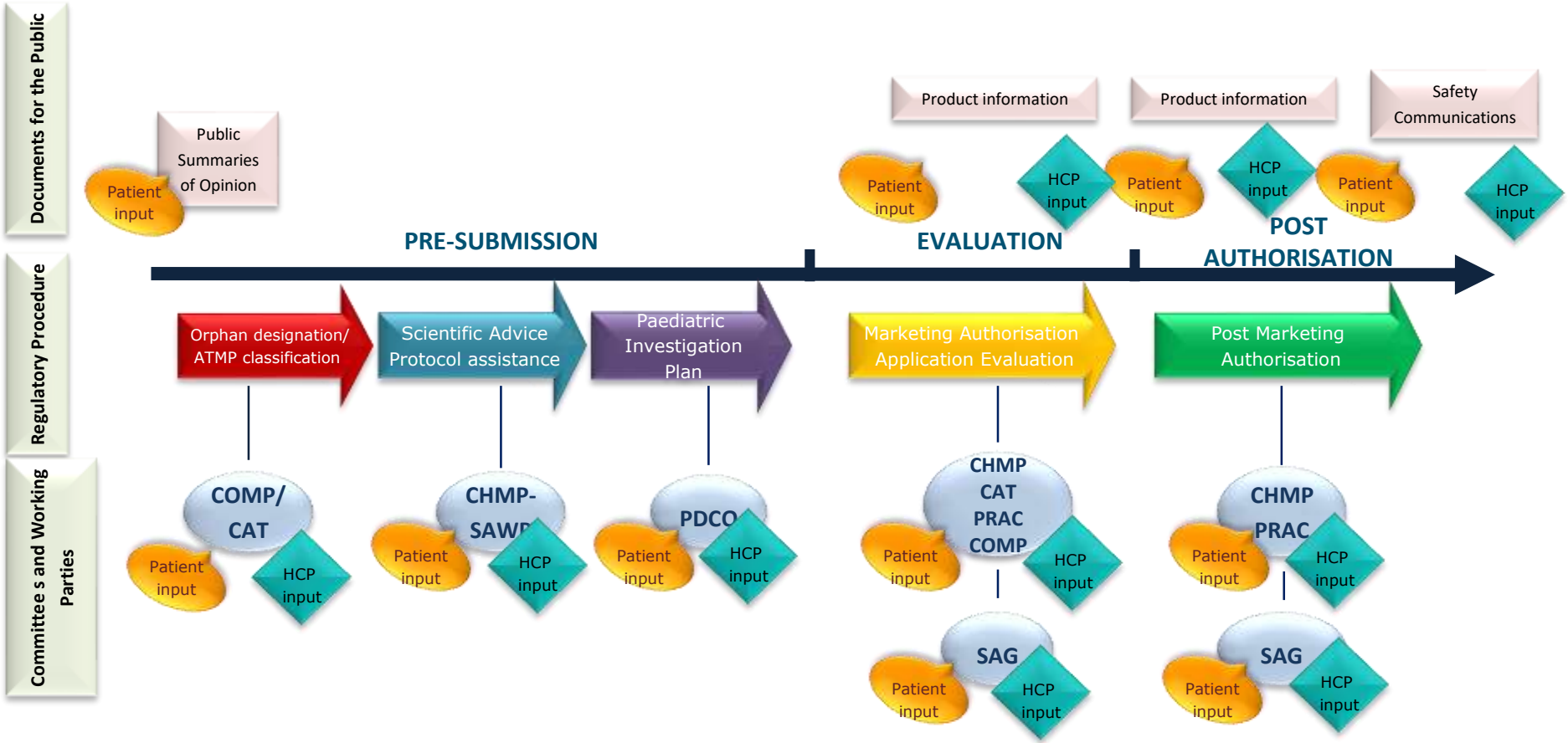
In 2015, EMA and the EU national competent authorities strengthened their collaboration to support medicine innovation and early development of new medicines in the EU by establishing the EU innovation network.

EMA and the HMA adopted the **mandate** of the EU Innovation Network in October 2016

EU Innovation Network Membership



Experimental therapies: ethics and regulatory science



CONCLUSIONS

Ethics and regulatory science offer critical support to sound experimental therapies

Science and technology advancing at unprecedented pace in life sciences put new challenges both to global and individual's choices

Emerging challenges deserve agile reflection, debate and participation within and across stakeholders of experimental medicine so that ethics is always interwoven with science and technologies applications

Thank you for your attention

Aknowledgments

Saint Raymond Agnes

Rodriguez Sanchez Beato Ana

Mihaescu Camelia Mihaela

Caromelle Aline

Further information

Marisa.Papaluca@ema.europa.eu

European Medicines Agency

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555

Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**

60 ROME PEACE DEMOCRACY SOLIDARITY

Core business of the Regulatory network is to…

Ensure seamless support at national and EU level

Encourage life-science innovation for methods and tools for drug development

Prepare the EMRN for successful support to priority medicines

Identifying challenging issues from emerging innovation

Developing EU methodology for innovation horizon scanning

Identifying best expertise

Developing new ways to better communicate with target groups

Developing training

Experimental therapies: ethics and regulatory science

EUROPEAN MEDICINES AGENCY

Autonomy	**Informed consent:** how is the subject informed and who's consent on what
	Patients involvement: essential component of modern experimental medicine
Beneficence	**Clinical trials:** evaluation, approval: ethical and conduct oversight First in Human: choice of subjects; trial design; stopping rules; Physiologically Based PK: M&S reduce uncertainties for dose finding Special populations: children, pregnant women, adults at risk, elderly, rare diseases Safety Committees rules
Non-maleficence	**Marketing Authorisation:** *Benefit/risks* evaluation, information, early access, medicines adaptive pathways to patients, Risk Management Plans, pharmacovigilance post-authorisation studies, Real Word Evidence
Distribution justice	**Equity of access:** early involvement of patients, special and vulnerable populations, health technology assessment bodies, payers in experimental medicines development consistent and independent information protection from falsified information and medicines,