Risk Management of Advanced Therapies

Dossier Requirements

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Content

- Legal basis
- When to submit EU Risk Management Plan
- Overview of the placeholders for risk management
- Structure of the EU Risk Management Plan for the Advanced Therapies
- Conclusions

Legislation (1)

Article 8 (3)(ia) of Directive 2001/83/EC requires the MAA to submit:

“a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce.”

-> EU RMP

Legislation (2)

Article 14 (1) of Regulation (EC) No 1394/2007 requires the MAA to submit:

"the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal products and of adverse reactions thereto."

-> Pharmacovigilance plan
-> Efficacy follow-up plan

Legislation (3)

Article 14 (2) of Regulation (EC) No 1394/2007 requires the MAA to submit:

"Where there is particular cause for concern, the Commission shall, on the advice of the Agency, require as part of the marketing authorisation that a **risk management system** designed to identify, characterise, prevent or minimise risks related to advanced therapy medicinal products, including an **evaluation of the effectiveness of that system**, be set up, or that **specific postmarketing studies** be carried out by the holder of the marketing authorisation and submitted for review to the Agency.."

-> all incorporated in EU RMP

Key Guidelines

- *Pharmacovigilance guidelines in Volume 9A*

  -> In particular the CHMP Guideline on Risk Management Systems (EMEA/CHMP/96268/2005) and its annexes which include ***the template for the Risk Management Plan****)*

- *Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (EMEA/149995/2008)*

The Pharmacovigilance System(1)

- All new applications
- Description in Module 1.8.1. of the application

- See “Guideline on Monitoring of Compliance with Pharmacovigilance Regulatory Obligations and Pharmacovigilance Inspections”

A Pharmacovigilance System serves as an essential infrastructure for a Risk Management System

The Pharmacovigilance System(2)

- **PhV Qualified Person (including back-up)**
- **Organisation and Infrastructure (incl. databases)**
- **Procedures in place:**
  - **Systems for collection, processing, quality control, coding, classification, medical review of ADRs, as well as signal detection and risk-benefit assessment (SOPs, Co-licensing agreements…)**
  - **Systems for reporting ADRs (expedited reports, PSURs…)**

The Risk Management System

- **Guideline on Risk Management Systems for Medicinal Products for Human Use**
  - **(Doc. Ref. EMEA/CHMP/96268/2005)**

- **Definition:**

« a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions »

=> Description in the Risk Management Plan

When is a risk management plan required? (1)

- New marketing authorisation
  - ✓New active substance
  - ✓A similar biological medicinal product
  - ✓Generic/hybrid where safety concern requiring additional risk minimisation activities has been identified with reference medicinal product

When is a risk management plan required? (2)

- Significant Changes to Marketing Autorisation
  - ✓ New pharmaceutical form
  - ✓ New route of administration
  - ✓ Significant change in an indication/patient population

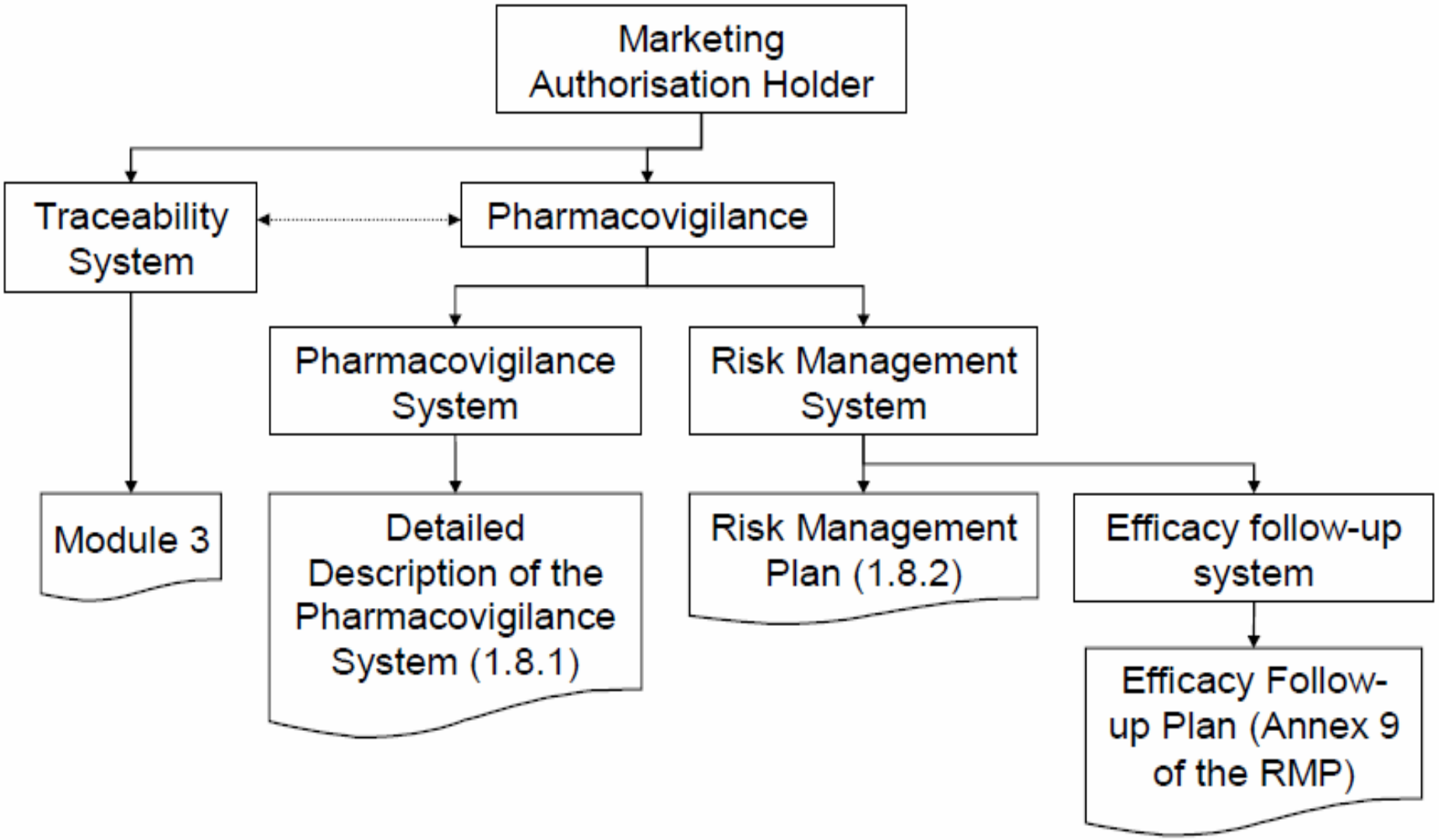
} Unless agreed not needed

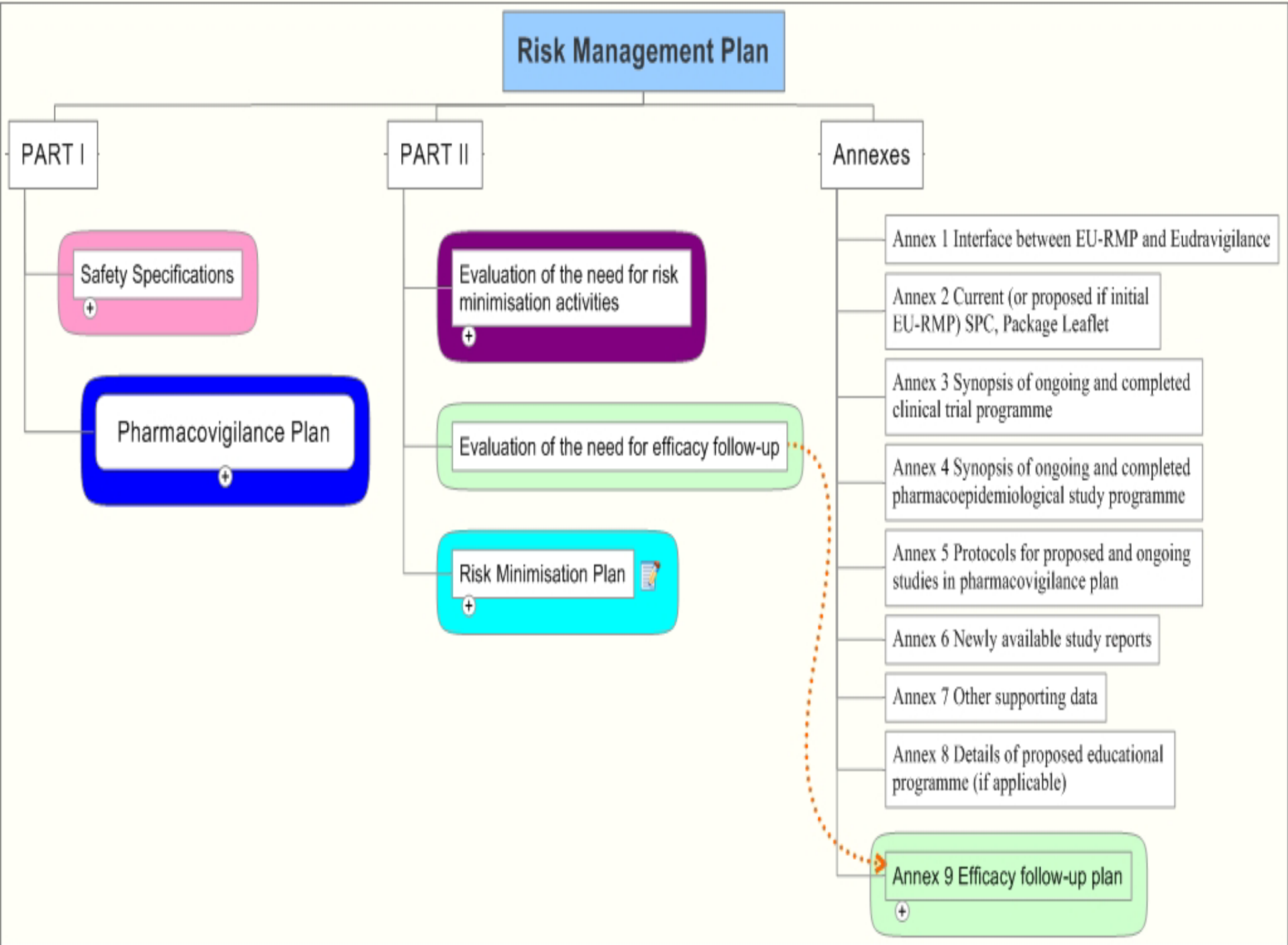
- On request from the Competent Authority
- On company initiative e.g., safety issue with a marketed medicine
- Update to previous EU-RMP

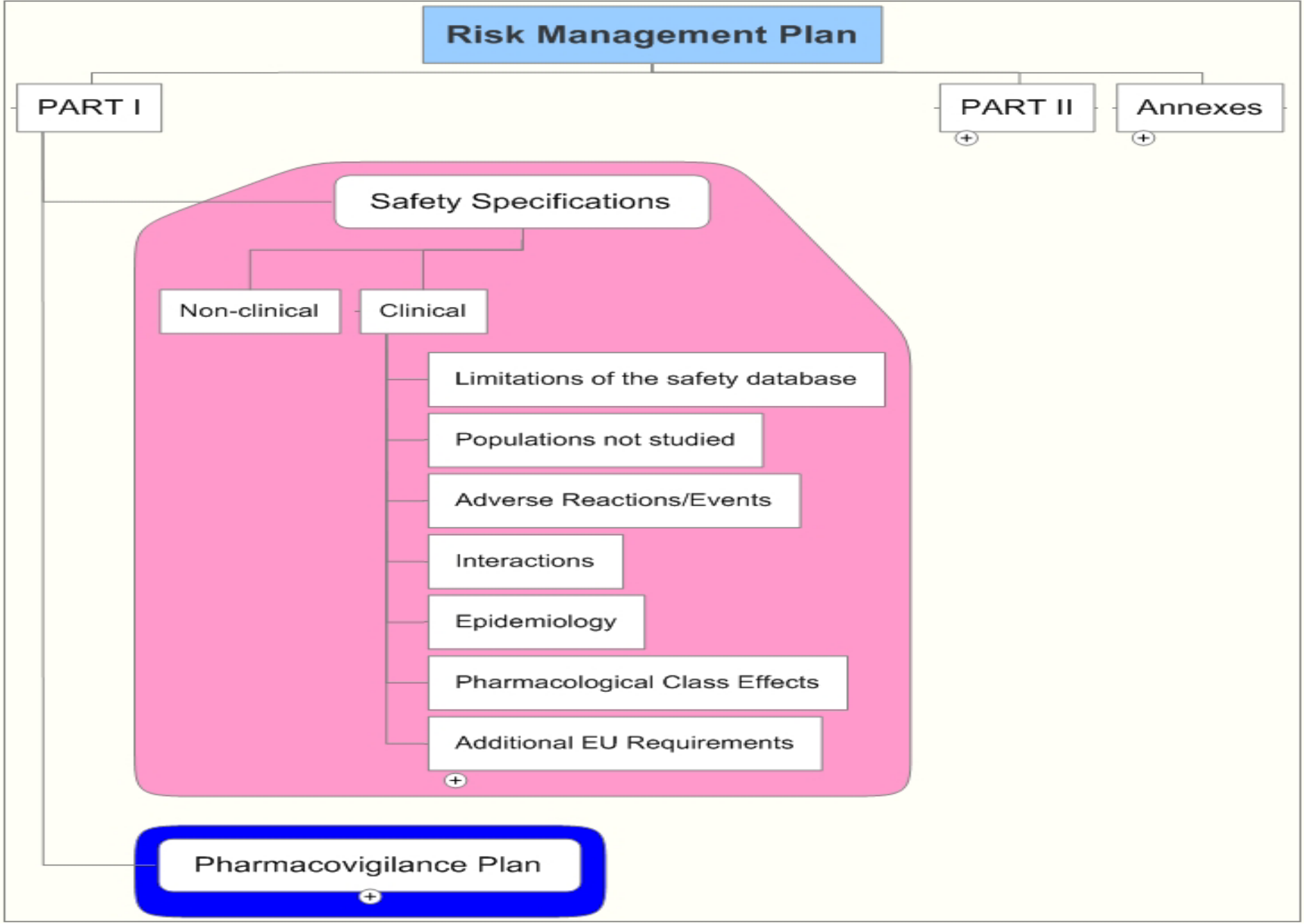
When EU-RMP MIGHT Also Be Required

- “Known active substances”
- Hybrid medicinal product where the changes compared with ref product suggest different risks
- Bibliographical applications
- “Fixed combination” applications

Post-authorisation surveillance systems



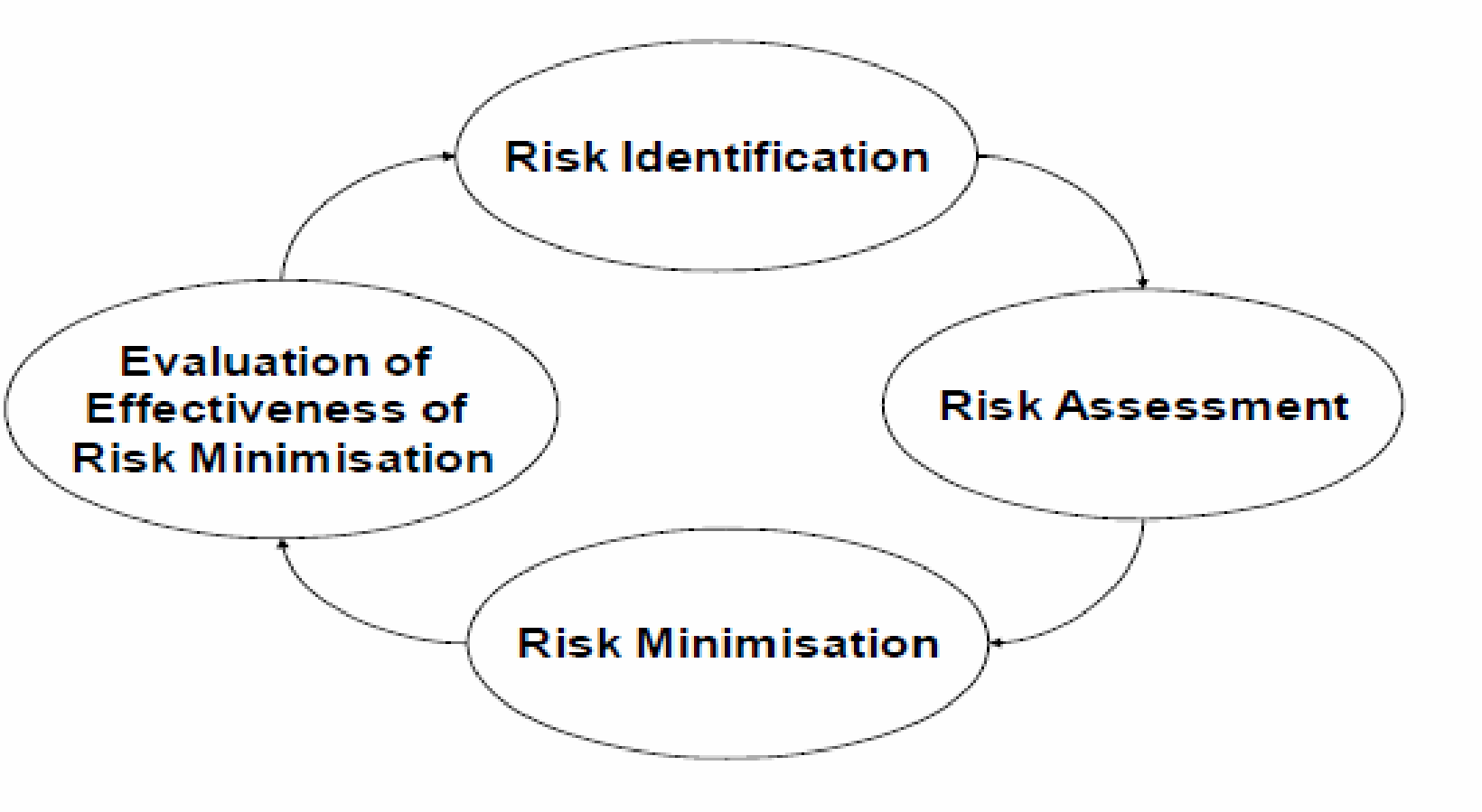

Risk Management Plan
PART I
PART II
Annexes
Safety Specifications
Pharmacovigilance Plan
Evaluation of the need for risk minimisation activities
Evaluation of the need for efficacy follow-up
Risk Minimisation Plan
Annex 1 Interface between EU-RMP and Eudravigilance
Annex 2 Current (or proposed if initial EU-RMP) SPC, Package Leaflet
Annex 3 Synopsis of ongoing and completed clinical trial programme
Annex 4 Synopsis of ongoing and completed pharmacoepidemiological study programme
Annex 5 Protocols for proposed and ongoing studies in pharmacovigilance plan
Annex 6 Newly available study reports
Annex 7 Other supporting data
Annex 8 Details of proposed educational programme (if applicable)
Annex 9 Efficacy follow-up plan


Risk Management Plan
PART I
PART II
Annexes
Safety Specifications
Non-clinical
Clinical
Limitations of the safety database
Populations not studied
Adverse Reactions/Events
Interactions
Epidemiology
Pharmacological Class Effects
Additional EU Requirements
Pharmacovigilance Plan

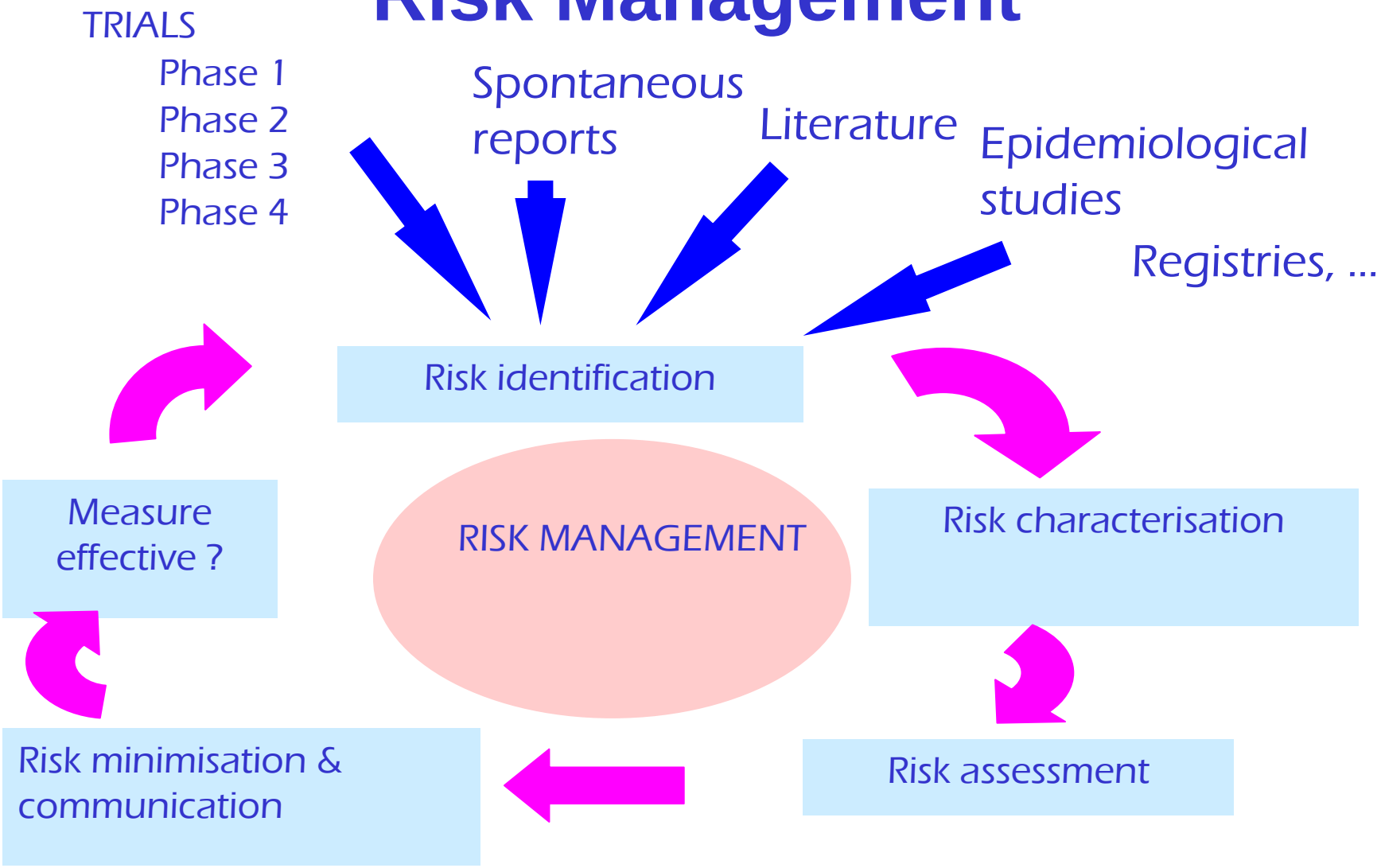
Specific chapter for ATMP

a. Flow-Chart of the logistics of the therapy (for instance, harvesting, transport, controls, manipulation, conditioning, administration, clinical follow-up…)
b. Risks to living donors (where applicable)
c. Risks to patients in relation to quality characteristics, storage and distribution of the product
d. Risks to patients related to administration procedures
e. Risks related to interaction of the product and the patient
f. Risks related to scaffolds, matrices and biomaterials
g. Risks related to persistence of the product in the patient
h. Risks to healthcare professionals, care givers, offspring and other close contacts with the product or its components, or with patients, presented in a summary fashion and based on the environmental risk assessment

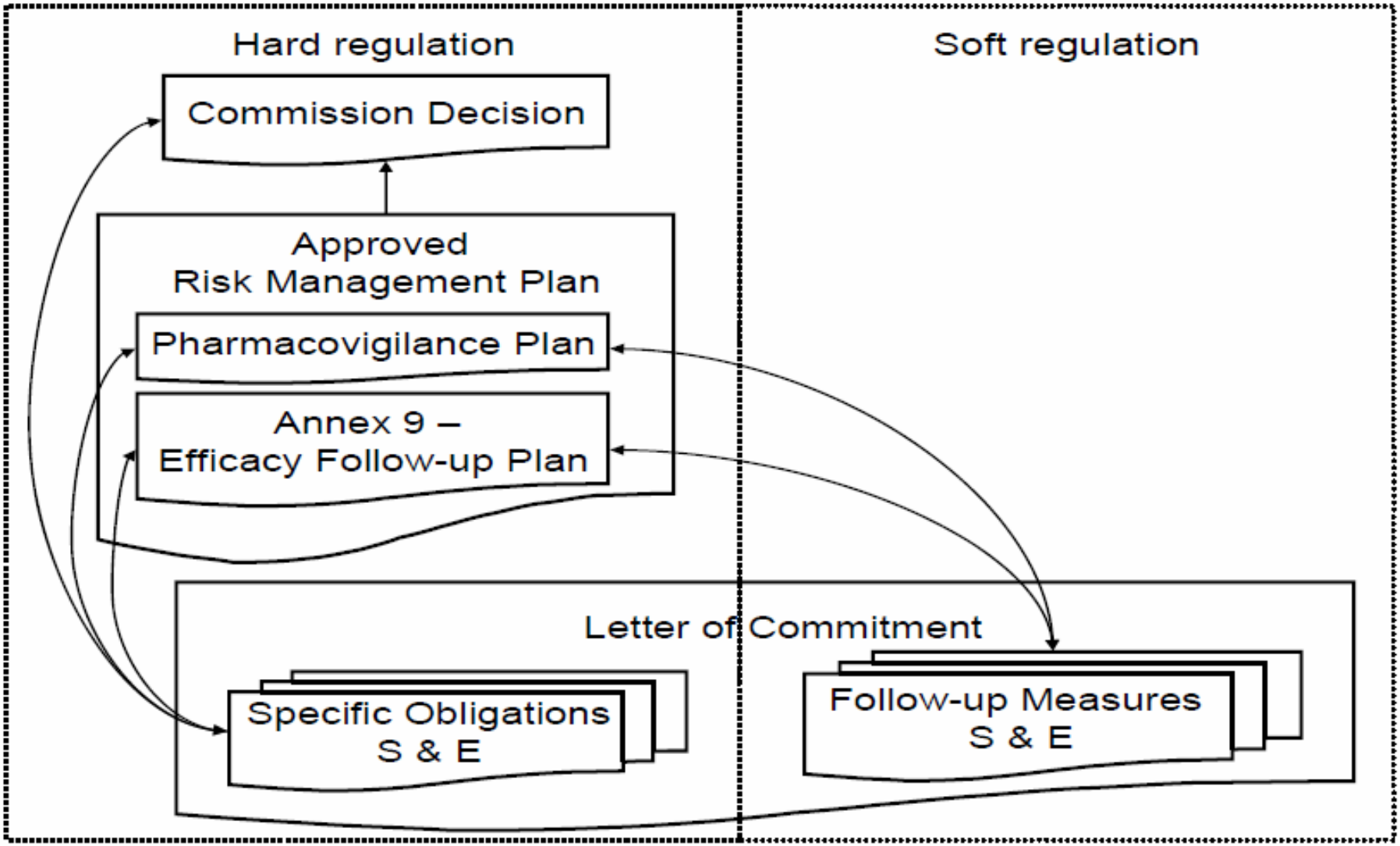
Risk Management Cycle



Risk Management



Overview of Post-authorisation commitments



Conclusion

- Maximum use of the existing systems and approaches
- Number of new provisions to accommodate specific characteristics of Advanced Therapies
- Flexible, living documents that are able to react quickly to evolving science