Where to Go: Developing a New Methodology for HEU-EFS in Europe

Proposed EU-EFS Process

EFS tailored templates and checklists

Performance metrics

Alexandra Poulsson | Norwegian Institute of Public Health

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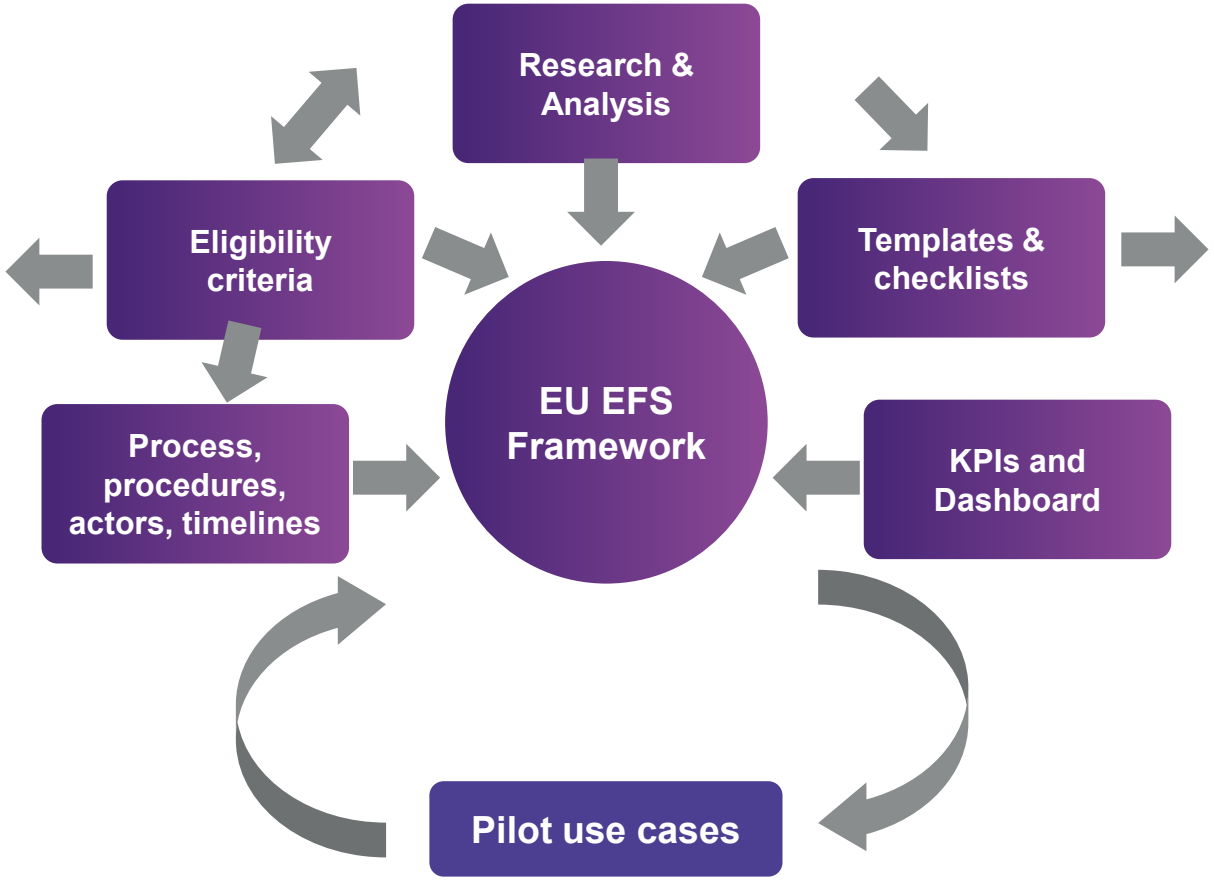
EU EFS Framework

- Technologies
- Patient conditions
- Level of pre-clinical evidence
- Trialists and clinical sites competence



- Clinical Investigation Plan
- Informed Consent Form
- Master Clinical Trial Agreement
- Insurance agreement

Synergies with Expert Panel Scientific Advice, HTAR JSC, Coordinated Assessment, draft MDCG Breakthrough Guidance, and other EU pathways.

Eligibility Criteria for the Pilots Technology

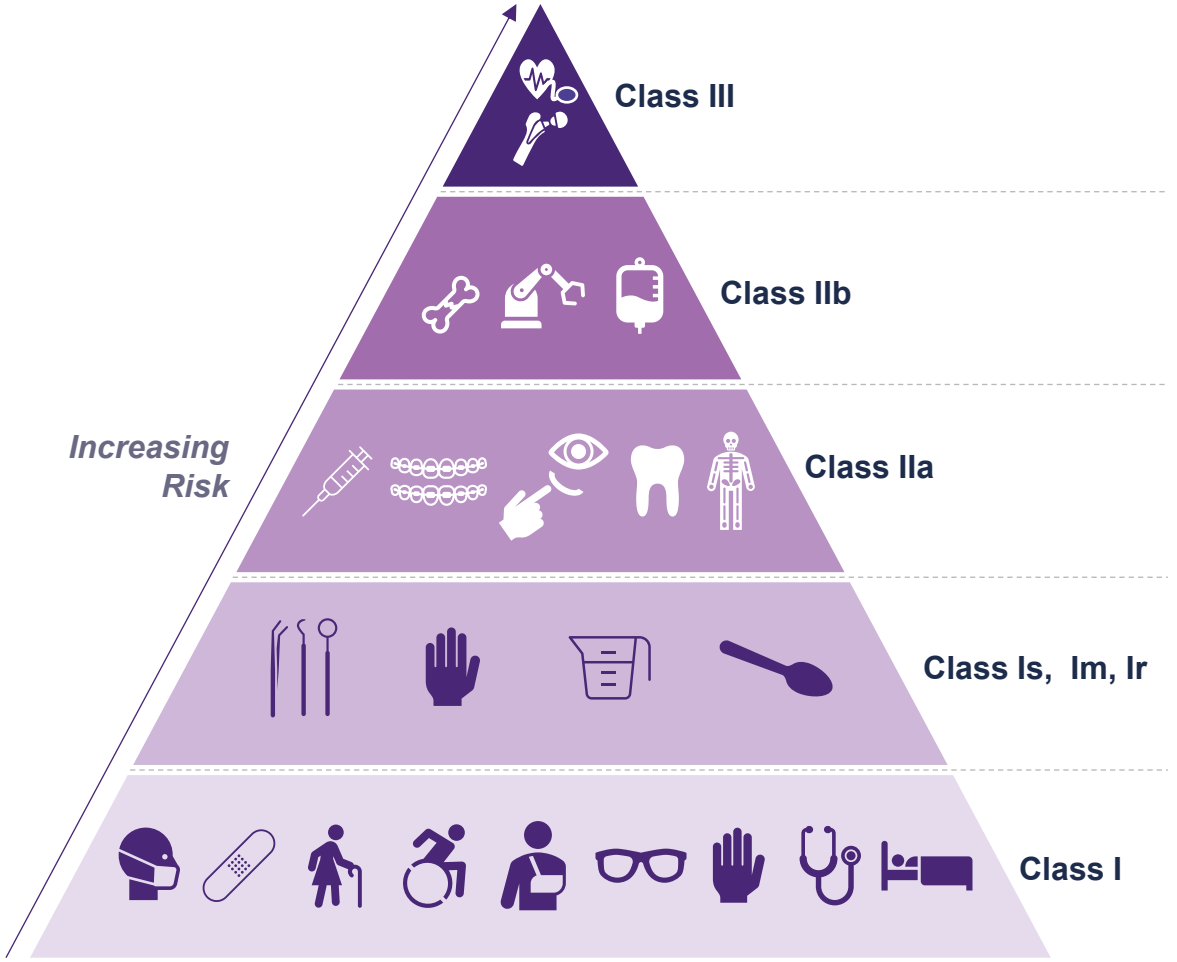
General criteria:

High-risk devices (Class III and Class IIb), where a clinical investigation will be required as part of the conformity assessment.

Breakthrough Device / Unmet Patients Needs

Anatomical Understanding

New / Expanded Intended Uses or Indications for Use for Patients



Level of pre-clinical evidence for EFS Pilots

GSPR* must be the **foundation for pre-clinical testing** performed for an EFS. **Pre-clinical testing will not be finalised** as the design may remain in **a continuous iterative phase**

Preclinical testing shall be **performed as far as possible** unless;

The **goal of the EFS** is to partially answer GSPRs

A **justification provided for limitations**, such as – further testing is not possible due to anatomy, physiology etc.

Concurrent testing can be performed without causing greater risk to the patients enrolled in the EFS.

Allow for **leveraging data from similar devices**

Pre-clinical testing is a challenge for start-ups;
To promote innovation in Europe, develop EFS guidance to help SMEs on
How to move from 'bench to bedside'.

*GSPR - General Safety and Performance Requirements

Clinical Sites and Clinical Expertise for EFS Pilots

The requirements defined by the MDR for sponsors, sites and investigators must be followed

Increase in **regulatory competence on EFS is beneficial for all parties** and a need for **ongoing dialogue between sponsors, personnel** involved in the EFS and NCA

Personnel conducting EFS should be qualified under ICH-GCP* and meet additional qualifications required at national level.

Ensure that the clinical site has **the capacity and equipment to offer adequate emergency care** and **support systems** during also after the EFS.

Clinical staff should have **experience in the therapeutic field**

Ensure **independence and transparency of clinical staff**

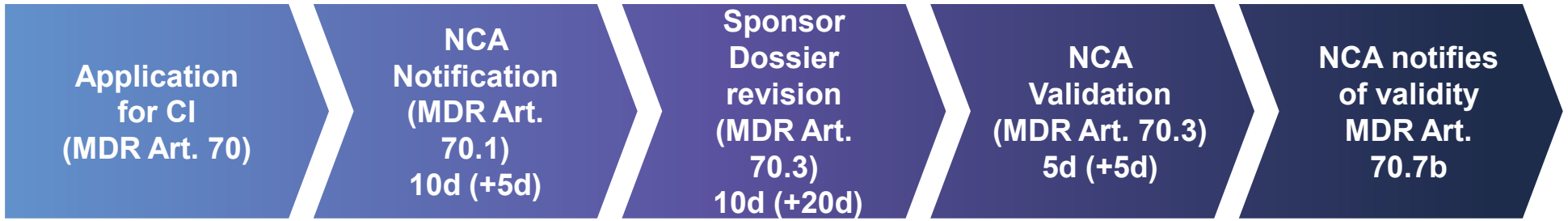
May have **dedicated units or personnel specifically** tasked with **coordinating regulatory submissions and contracts.**

*ICH-GCP – International Council for Hamonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice

EFS are pre-market CIs which fall under Art. 70 of MDR

CI for invasive IIa, IIb and all class III devices

CI for class I and non-invasive IIa and IIb devices



*For devices covered by Art. 62.
Abbreviations Art. = article of the MDR, d=days, CIP =Clinical Investigation Plan, IB = Investigator's Brochure, ICF = informed consent form),

Process Goals and Considerations

Enhance Early Dialogue options

Accelerated EFS Process (~30% reduction in review times)

Streamlined templates / checklists and performance metrics

Parallel NCA & EC review where possible

- ✓ Timely
- ✓ Efficiency
- ✓ Collaboration

EU Process Overview

Pre-Submission | **Submission & Review**

Contact Point → **Early Dialogue** → **Submission** → **Validation** → **Review**

Pre-submission phase

- Contact point early in the process to allow for planning and resource allocation
- Multi stakeholder early dialogue for sponsor, NCA and where appropriate and relevant Ethics Committee, experts on the NCA, Principal investigator of clinical site. Option to invite other Member States if EFS is conducted in multiple countries

National Competent Authority (NCA)

Initial "Validation" Phase → completeness of submission file

- NCA Assessment time
- Proceed to Review Phase or Request for Information (RFI)
- RFI Cycle time for Sponsor and NCA

Review Phase → Scientific Review of submission file

- NCA review time, including utilizing a “stop-clock“ approach, and encouraging “rolling review process“ to facilitate timely review
- Approval or request for Information (RFI)
- RFI Cycle time for sponsor and NCA

Target 30% Reduction in Overall Process Timelines Compared to Current MDR

Pre-Submission Details

Contact Point → Early Dialogue

Contact Point

- Alerts NCA (and other recipients) to incoming file
- Identifies key principles of device technology
- Outlines qualifications for accelerated review
- Cycle timing: 1-2 weeks

Early Dialogue (optional)

- Opportunity to have targeted discussions related to the device, patient population, etc.
- Pre-submission to include appropriate background information
- Cycle timing: 30-60 days

Submission: Validation Details

Submission → Validation

Current MDR
(Article 70) Timing
(10 - 55 days)

- NCA Assessment: 10 – **15** days
- Sponsor response to identified gaps: 10 – **30** days
- Final NCA decision: 5 – **10** days

Proposed Accelerated
(HEU-EFS) Timing
(7 - 39 days)

- NCA Assessment: 7 – **12** days
- Sponsor response to identified gaps: 7 – **17** days
- Final NCA decision: 5 – **10** days

Submission: Review Details

Submission → Review

Current MDR (Article 70) Timing (45 - 65 days)	Proposed Accelerated (HEU-EFS) Timing (30 - 45 days)
• NCA Assessment: 45 – **65** days • Sponsor response to identified gaps: Timing not specified • Final NCA decision: Utilization of remaining clock	• NCA Assessment: 30 – **45** days • Deficiency Communication: – Rolling Review/Interactive Questions approach – "Stop Clock" approach – "Approval with Conditions" approach • Sponsor response to identified gaps: rapidly, be prepared • Final NCA decision: Utilization of remaining clock

HEU-EFS develop standardized checklists and template

Clinical Investigation Plan

- **The template** based heavily on MDCG 2024-3 but tailored to EFS
- **The checklist** aids sponsors **internally** verify that **CIP is completed appropriately** specifically for EFS

Informed Consent Form

- **The template based on MDR** provides a standardised format for sponsors — particularly SMEs — that may lack internal documentation resources.
- **The checklist** aids sponsors **internally** to verify that patient requirements are met, for the application process for the NCA and EC approval to be **compliant** with **relevant regulation**.

Master Clinical Trial Agreement

- **The checklist** ensures all relevant and EFS-specific contractual elements are included.

Insurance Agreement

- **The guidance** is a practical solution given that the insurance agreement is typically non-negotiable.
- It serves as a reference document to ensure inclusion of the **minimum essential elements required.**

KPIs collected via online forms from sponsors of the EFS pilots

	Form #1	Form #2	Form #3	Form #4
	Before the start of EFS pilot	**After EFS application has been submitted to NCA**	**After EFS application has been validated by NCA**	**After EFS pilot has been completed**
Main planned KPIs	• EFS submitted – *Per country, per year* • EFS submitted by SMEs – *Per country, per year* • NCAs involved in EFS assessment • EFS involving patient / patient assoc. in study design	• Dialogue – *Type* • Clinical sites involved in EFS – *Per country, per year (EU only)* • Single-centre, multi-centre, multi-country EFS • Risk class • Health conditions • Use of PROMs and PREMs	• EFS approved – *Total, per country, per year* • EFS approved by SMEs – *Total, per country, per year* • Time for EFS approval • EFS applications rejected • List of ethics committee involved in EFS assessment • Time from ethics committee submission to approval	• Time from clinical site sign. to 1st patient enrolled • # of patients enrolled in EFS • % of EFS transitioned to other CIs • EFS terminated, withdrawn, or suspended • Additional pre-market CIs after EFS termination, withdrawn, or suspension

www.heuefs.eu

info@heuefs.eu

@HEU-EFS

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