The EU-MDD

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Topics

- Clinical Evaluation
- Post-market Clinical Follow-up (PMCF)
- EU Vigilance Reports
- Field Safety Corrective Actions & FSN
- Trend Reporting
- Questions

Clinical Evaluation

Directives and Guidance

- In the EU, medical devices fall under one of three directives
- Both the Medical Device Directive (MDD) and the Active Implantable Medical Device Directive (AIMDD) require Clinical Evaluation
- The *In Vitro Diagnostic Directive* (IVDD) does not
- In addition, there is a guidance document that provides additional information on conducting and documenting a Clinical Evaluation
- In June 2016, the EU issued MedDev 2.7/1 Rev. 4 *Clinical Evaluation: A Guide For Manufacturers And Notified Bodies Under Directives 93/42/EEC and 90/385/EEC*

Role of Clinical Evaluation

- Clinical Evaluation collects, appraises, and analyzes clinical data to confirm compliance with Essential Requirements in the product directive.
- Clinical Evaluation applies to all device classes.
- Clinical Evaluation should specify the risk and benefits of the device (nature, probability, extent, duration, and frequency).
- The result will include a determination of the risk/benefit profile and demonstration that, based on current knowledge, the profile is acceptable.

Medical Device Directive

- Clinical Evaluation addresses the issues raised in Annex I, Sections 1, 3, and 6
- The evaluation follows defined and methodologically sound procedures based on Annex X
- When it is not appropriate to base demonstration of an essential requirement on clinical evaluation, document the justification according to Annex X, Section 1.1.d

MDD Annex X

Use of Clinical Data

- Under normal use conditions the evaluation of the device for Annex I Section 1 and Section 3 must rely on clinical data.
  - Section 1 concerns design and manufacture to avoid compromise of:
    - Patient clinical condition or safety
    - User health or safety
    - Other person's health or safety
  - Section 3 concerns:
    - Devices performing as intended
    - Suitably designed, manufactured, and packaged

Source MDD Annex X, section 1.1

Use of Clinical Data

- Any evaluation of side effects and risk / benefit ratio for Annex I Section 6 must rely on clinical data
  - “Any undesirable side-effect must constitute an acceptable risk when weighed against the performances intended.”

Source MDD Annex X, section 1.1

What is Clinical Data?

- *Clinical data* means the safety and/or performance information that is generated from the use of a device.

  Clinical data are sourced from:
  - clinical investigation(s) of the device concerned; or
  - clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated; or
  - published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated;

Source MDD Article 1 Clause 2(k)

What is Clinical Evaluation?

- *Clinical evaluation* means the evaluation of clinical data

- Clinical evaluation must follow a defined and methodologically sound procedure based on:
  - Relevant scientific literature OR
  - Results of all clinical investigations OR
  - A combination of the two

Source MDD Annex X, section 1.1

Clinical Evaluation

- MDD Annex I, Section 6a
  - Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.

Role of Post-Market Surveillance

- Annex X, Section 1.1b requires documentation of the clinical evaluation and its outcome.

- Annex X Section 1.1c requires, “The clinical evaluation and its documentation must be actively updated with data obtained from the post-market surveillance.”

MEDDEV 2.7/1 Rev. 4

MEDDEV 2.7/1 Rev. 4

- MEDDEV 2.7/1 Rev. 4 *Clinical Evaluation: Guide for Manufacturers and Notified Bodies*
- This version was issued in June 2016 and went into effect immediately
- It is significantly changed from Rev. 3
- Obtain a copy from https://ec.europa.eu/growth/sectors/medical-devices/guidance_en

Definitions

- MEDDEV 2.7/1 Rev. 4 includes some valuable definitions
  - *Clinical Data*: The safety and/or performance information that is generated from the clinical use of a device
  - *Clinical Evaluation*: A methodologically sound ongoing procedure to collect, appraise, and analyze clinical data pertaining to a medical device and to evaluate whether there is sufficient clinical evidence to confirm compliance with relevant essential requirements for safety and performance when using the device according to the manufacturer's Instructions for Use.
  - *Clinical Evidence*: The clinical data and the clinical evaluation report pertaining to a medical device.

Definitions (cont.)

- MEDDEV 2.7/1 Rev. 4 includes some valuable definitions
  - *Clinical Investigation*: Systematic investigation in one or more human subjects, undertaken to assess the safety or performance of a medical device.
  - *Clinical Performance*: Behavior of a medical device or response of the subject(s) to that medical device in relation to its intended use, when correctly applied to appropriate subject(s).
  - *Clinical Safety*: Freedom from unacceptable clinical risks, when using the device according to the manufacturer's Instructions for Use.
  - *Risk*: Combination of the probability of occurrence of harm and the severity of that harm.

Definitions (cont.)

- MEDDEV 2.7/1 Rev. 4 includes some valuable definitions
  - *PMCF study*: A study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (*i.e.,* residual risks) of a device when used in accordance with its approved labelling. [MEDDEV 2.12/2 Rev. 2]
  - *PMCF plan*: The documented, proactive, organized methods and procedures set up by the manufacturer to collect clinical data based on the use of a CE-marked device corresponding to a particular design dossier or on the use of a group of medical devices belonging to the same subcategory or generic device group as defined in [the MDD] The objective is to confirm clinical performance and safety throughout the expected lifetime of the medical device, the acceptability of identified risks and to detect emerging risks on the basis of factual evidence. [MEDDEV 2.12/2 Rev. 2]

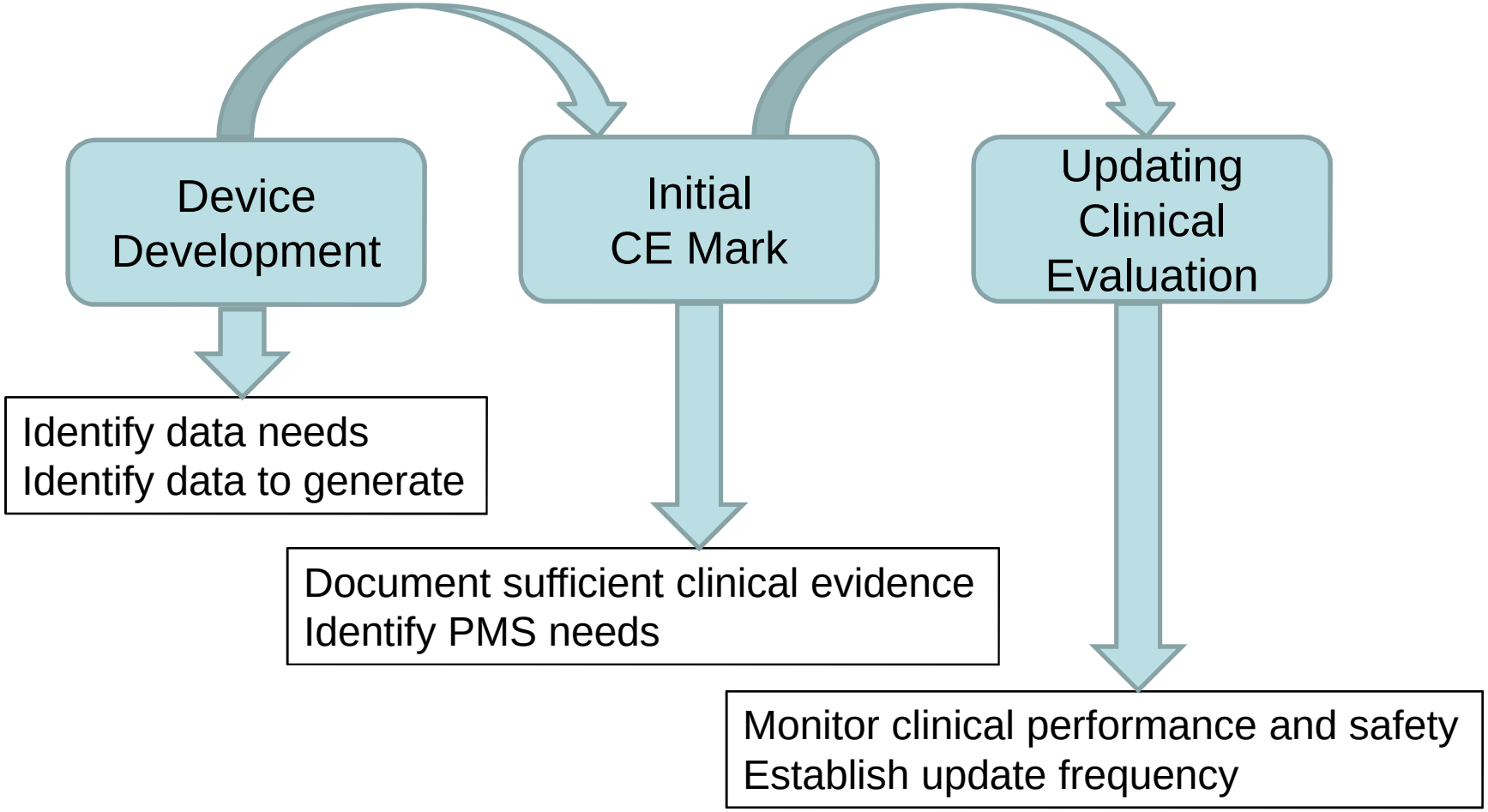
Clinical Evaluation Life Cycle

Life Cycle

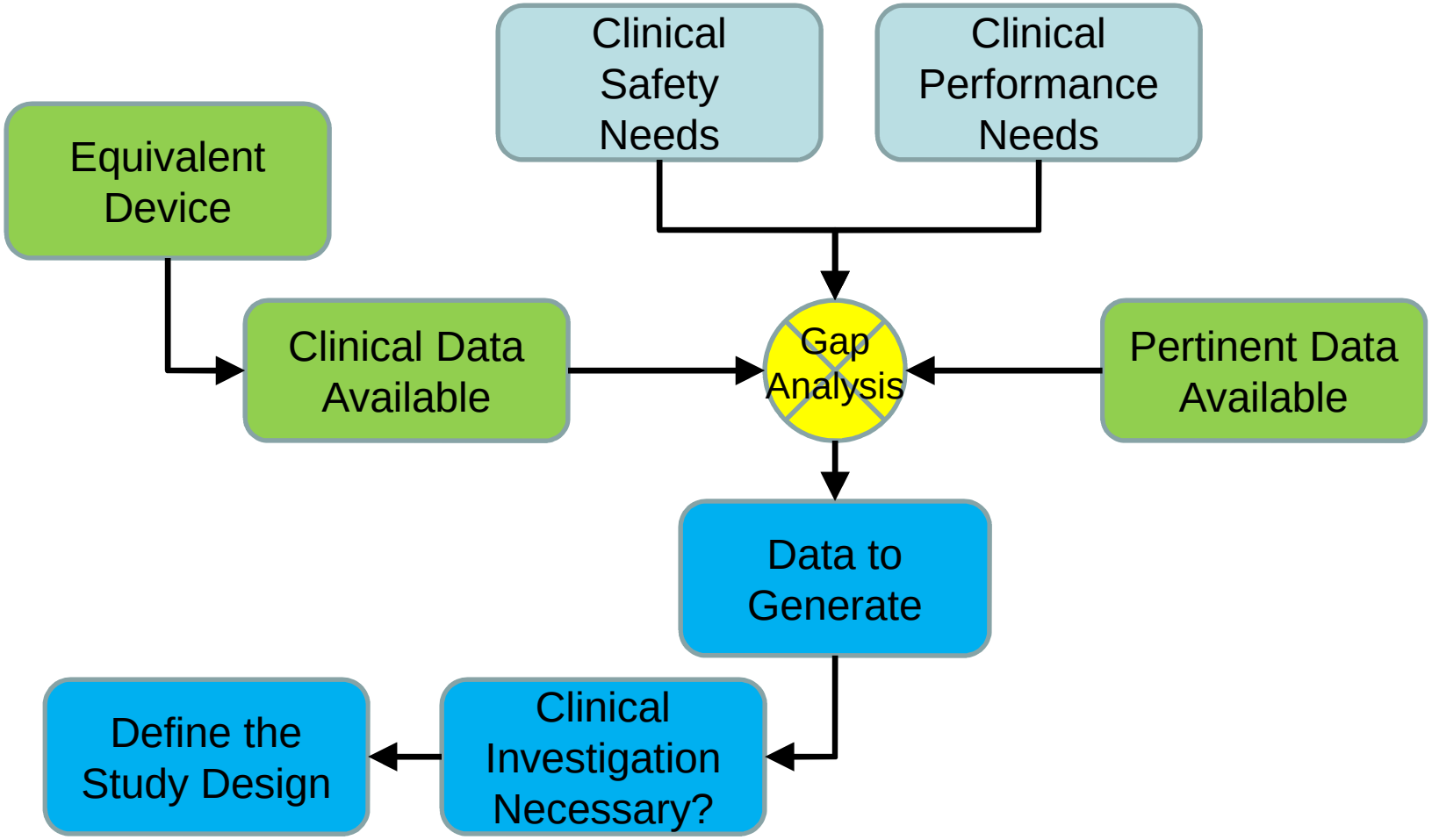
- Clinical Evaluation is a life-cycle activity that, similar to Risk Management, covers all phases in the life of a medical device, from the initial conception to final decommissioning and disposal

- The MedDev identifies three phases:
  - Device Development
  - Initial CE marking
  - Post-market or Post-production

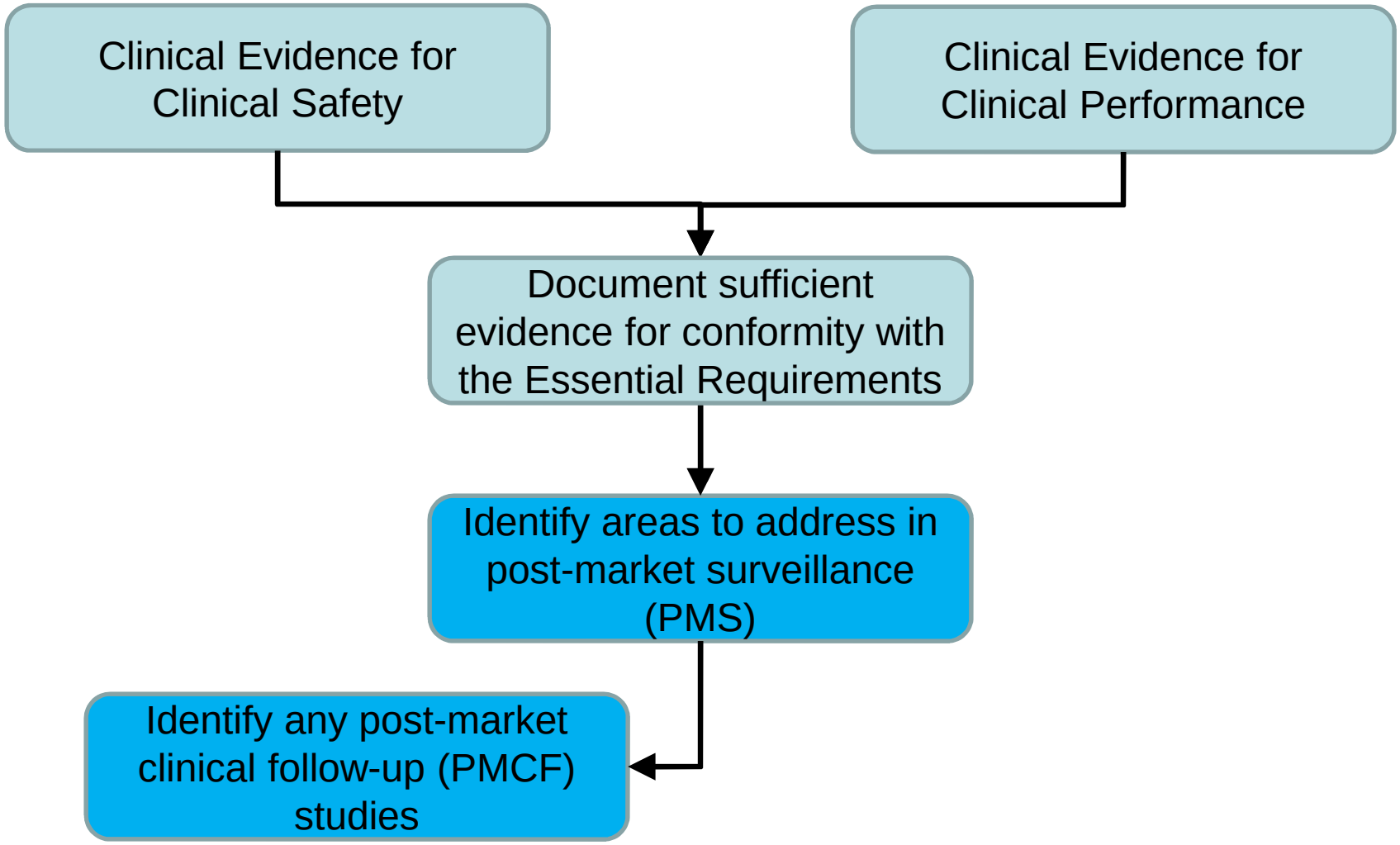
Life Cycle


Device Development
Initial CE Mark
Updating Clinical Evaluation
Identify data needs
Identify data to generate
Document sufficient clinical evidence
Identify PMS needs
Monitor clinical performance and safety
Establish update frequency

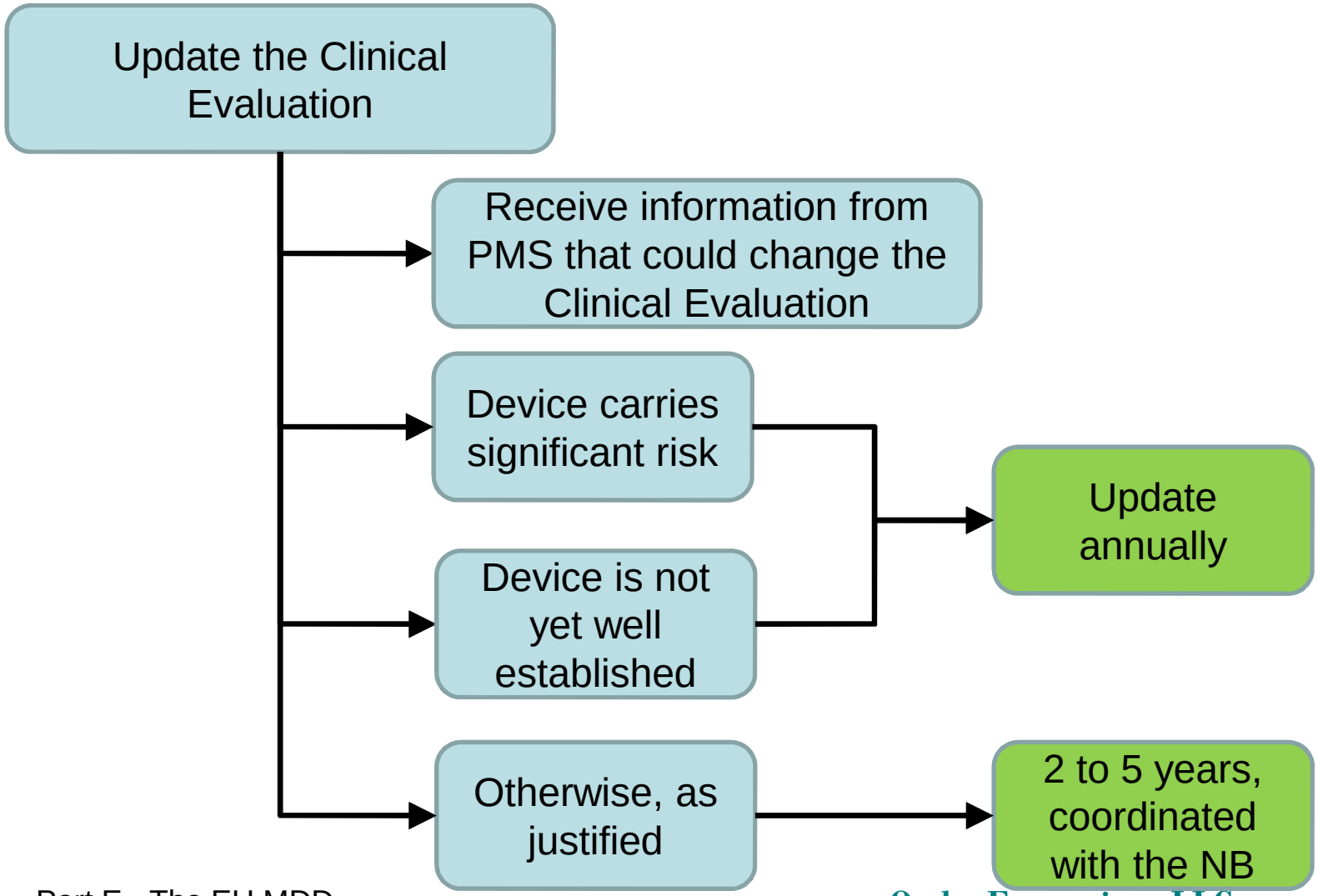
Device Development



Initial CE Marking



Clinical Evaluation Updates



Post-market Clinical Follow-up (PMCF)

MDD Annex II, Section 5.2

- The manufacturer must authorize the notified body to carry out all the necessary inspections and supply it with all relevant information, in particular:
  - the documentation on the quality system,
  - the data stipulated in the part of the quality system relating to design, such as the results of analyses, calculations, tests, the solutions adopted as referred to in Annex I, Chapter I, Section 2, pre-clinical and clinical evaluation, post-market clinical follow-up plan and the results of the post-market clinical follow-up, if applicable, *etc*.
  - the data stipulated in the part of the quality system relating to manufacture, such as inspection reports and test data, calibration data, qualification reports of the personnel concerned, *etc*.

PMCF Needs

- Determine any needs for PMCF studies:
  - Describe the residual risk (See EN ISO 14971:2012, Clause 7)
  - Identify any uncertainties or unanswered questions
  - Determine the need for information on:
    - Rare complications
    - Medium and long term performance
    - Safety in wide-spread use

- Develop and conduct PMCF studies following MedDev 2.12/2

MedDev 2.12/2

- *Post-market clinical follow-up (PMCF) Study* means a study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (*i.e.,* residual risks) of a device when used in accordance with its approved labelling.

- *PMCF Plan* means the documented, proactive, organized methods, and procedures set up by the manufacturer to collect clinical data based on the use of a CE-marked device corresponding to a particular design dossier or on the use of a group of medical devices belonging to the same subcategory or generic device group as defined in [the MDD]. The objective is to confirm clinical performance and safety throughout the expected lifetime of the medical device, the acceptability of identified risks and to detect emerging risks on the basis of factual evidence.

PMCF Indicated?

- Following a proper premarket clinical evaluation, the decision to conduct PMCF studies must be based on the identification of possible residual risks and/or unclarity on long term clinical performance that may impact the benefit/risk ratio.
- PMCF studies may review issues such as long-term performance and/or safety, the occurrence of clinical events (e.g. delayed hypersensitivity reactions, thrombosis), events specific to defined patient populations, or the performance and/or safety of the device in a more representative population of users and patients.

- PMCF studies may not be required when the medium/long-term safety and clinical performance are already known from previous use of the device or where other appropriate post-market surveillance activities would provide sufficient data to address the risks.

PMCF Plan

- PMCF studies must be outlined as a well designed clinical investigation plan or study plan, and, as appropriate, include:
  - clearly stated research questions, objectives, and related endpoints
  - scientifically sound design with an appropriate rationale and statistical analysis plan
  - a plan for conduct according to the appropriate standards
  - a plan for an analysis of the data and for drawing appropriate conclusions

EU Vigilance Reports

MEDDEV 2.12/1 Rev. 8

Issued January 2013

Applicable as of July 2013

Incident

- 4.10 INCIDENT
- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Indirect Harm

- 4.11 INDIRECT HARM
- In the majority of cases, diagnostic devices, IVDs, and IVF/ART medical devices will, due to their intended use, not directly lead to physical injury or damage to health of people. These devices are more likely to lead to indirect harm rather than to direct harm. Harm may occur as a consequence of the medical decision, action taken/not taken on the basis of information or results provided by the device or as a consequence of the treatment of cells (*e.g.,* gametes and embryos in the case of IVF/ART devices) or organs outside of the human body that will later be transferred to a patient.

Deterioration In State Of Health

- A serious deterioration in state of health can include (non exhaustive list):

  a) life-threatening illness,

  b) permanent impairment of a body function or permanent damage to a body structure,

  c) a condition necessitating medical or surgical intervention to prevent a) or b),

  d) any indirect harm as a consequence of an incorrect diagnostic or IVD test result or as a consequence of the use of an IVF/ART device when used within manufacturer´s instructions for use, or

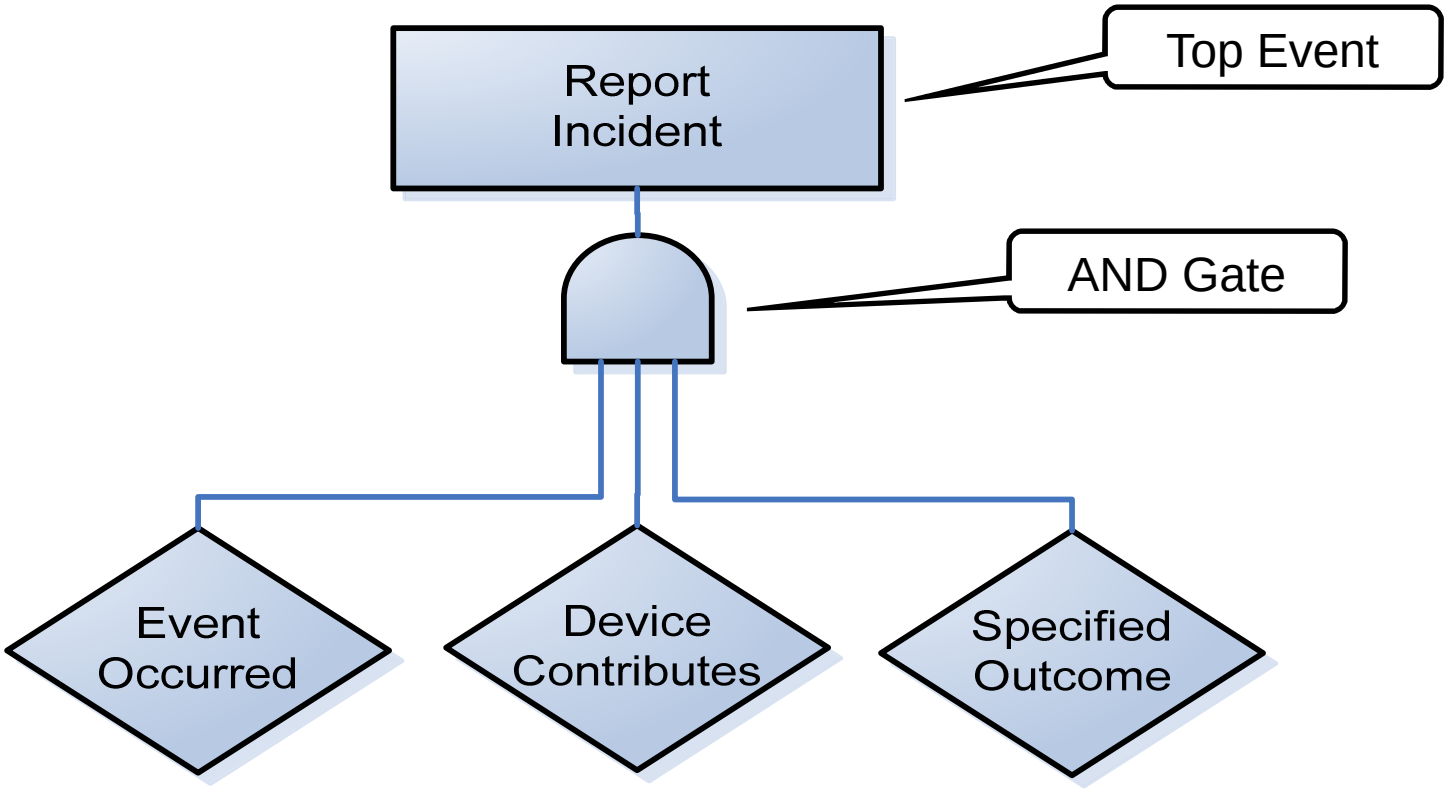
  e) foetal distress, foetal death or any congenital abnormality or birth defects

What to Report

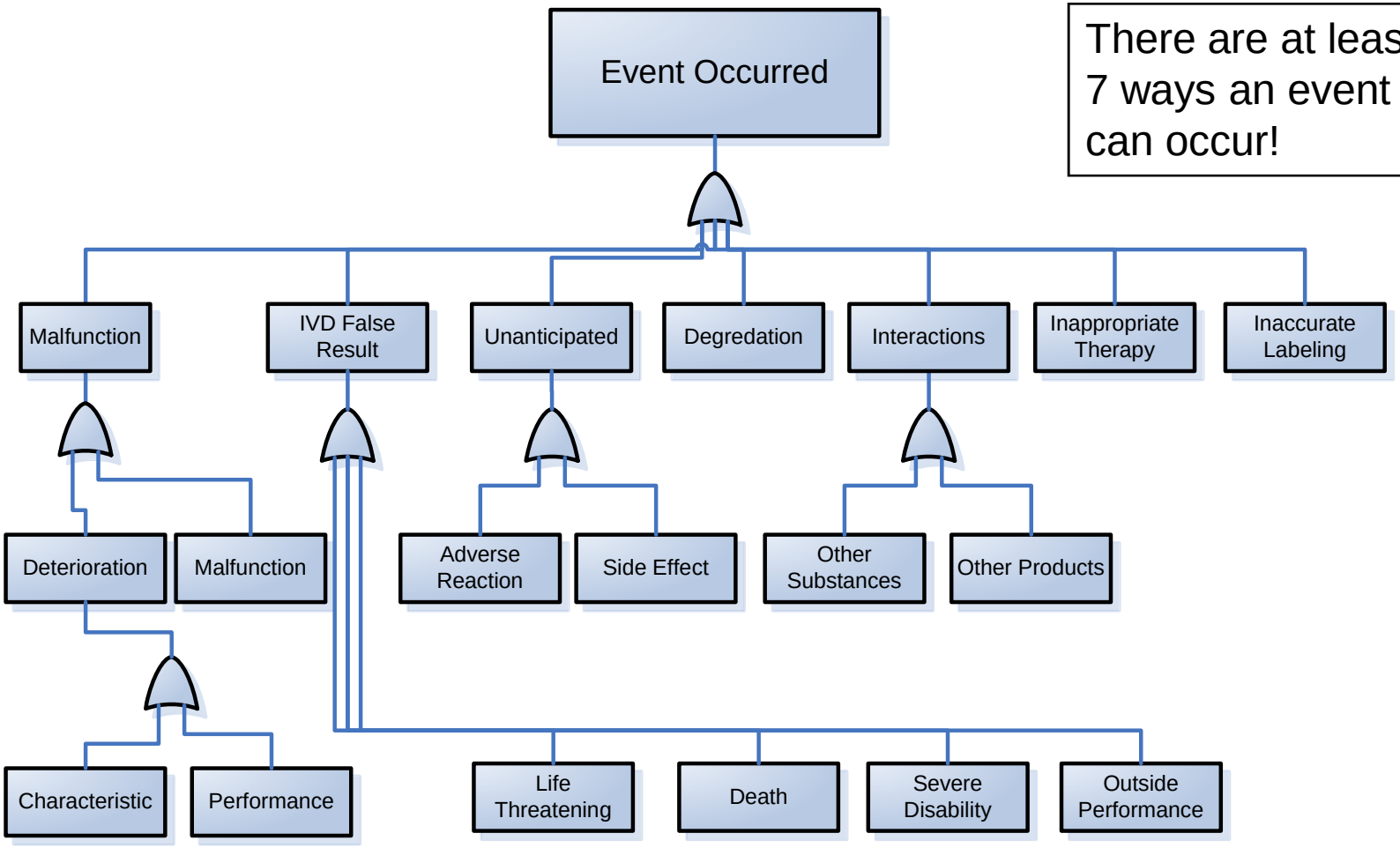
- An event is reportable when it meets all three criteria
  A. An event has occurred
  B. The manufacturer's device is suspected to be a contributory cause of the incident
  C. The event led, or might have led, to one of the following outcomes:
     - Death of a patient, user, or other person
     - Serious deterioration in the state of health of a patient, user, or other person

Incident Report Trigger

FTA View

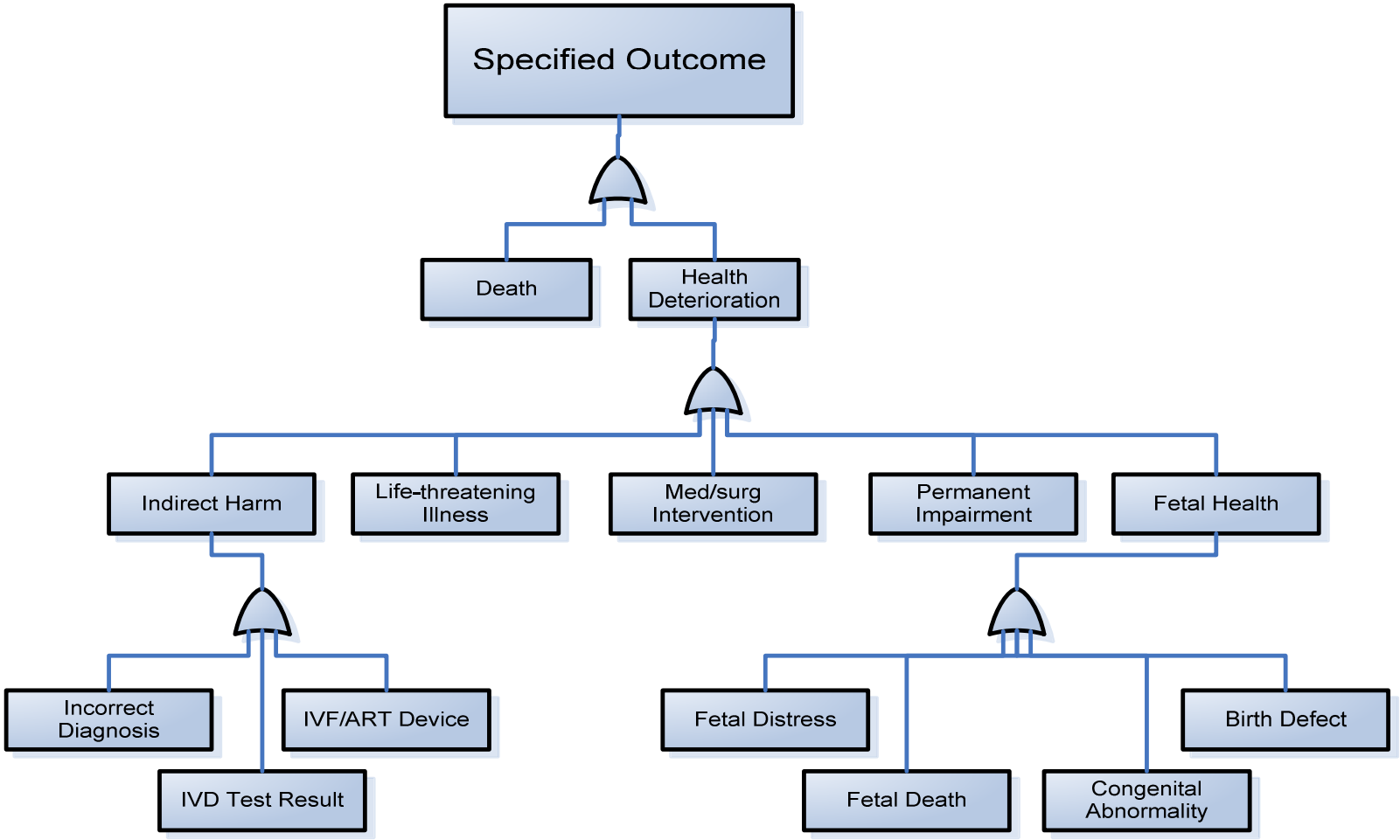


Event Occurred



There are at least 7 ways an event can occur!

Specified Outcome



When to Report

Incident Type	Timeline
Serious public health threat	Immediately, but not later than 2 calendar days
Death or unanticipated serious deterioration in state of health	Immediately, but not later than 10 elapsed calendar days
Other	Immediately but not later than 30 elapsed calendar days

Vigilance Record Retention

- Records of incident reports shall be retained to enable the investigation to be reopened if necessary, and to facilitate systems for trend analysis.

Field Safety Corrective Action
Field Safety Notice

MEDDEV 2.12/1 Rev. 8

Issued January 2013

Applicable as of July 2013

Definition – FSCA

- 4.6 Field Safety Corrective Action (FSCA)
- A Field Safety Corrective Action is an action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. Such actions, whether associated with direct or indirect harm, should be reported and should be notified via a Field Safety Notice.

Definition – FSN

- 4.7 Field Safety Notice (FSN)
- A communication to customers and/or users sent out by a manufacturer or its representative in relation to a Field Safety Corrective Action.

Considerations

- This is a systemic recall of a device
- Typical reasons include:
  - Malfunction of the device
  - Deterioration in performance or characteristics
  - Inadequate instructions for use
- Removal for commercial non-safety reasons are not included.

Recommended Formats

- MEDDEV 2.12-1 rev 8 includes recommended formats for an FSCA and an FSN
  - Annex 4 Report Form for Field Safety Corrective Action
  - Annex 5 Template for a Field Safety Notice

Reporting

- Issue the notification to the Competent Authorities of all affected countries at the same time.
- Issue the notification to the National Competent Authority responsible for the manufacturer or authorized representative.
- Inform any Notified Body involved in the conformity assessment.
- Inform customers and users using a Field Safety Notice.

Trend Reporting

MEDDEV 2.12/1 Rev. 8

Issued January 2013

Applicable as of July 2013

Trend Reporting

- 4.18 Trend Reporting
- A reporting type used by the manufacturer when a significant increase in events not normally considered to be incidents according to section 5.1.3. occurred and for which pre-defined trigger levels are used to determine the threshold for reporting.

- Appendix C of GHTF/SG2/N54R8:2006 *Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices* provides useful guidance.

- GHTF guidance documents are available at www.imdrf.org

Not Reportable

- Section 5.1.3 lists conditions where vigilance reporting is not usually required
  - Deficiency of a device found by the user prior to its use
  - Event caused by patient conditions
  - Service life or shelf-life of the medical device exceeded
  - Protection against a fault functioned correctly
  - Expected and foreseeable side effects
  - Negligible likelihood of occurrence of death or serious deterioration in state of health

Trend Report

- Trigger: Significant increase in or trend of event or incidents usually excluded from Incident Reporting (5.1.4)
- Timing: Not stated, assume Immediately
- Recipient: National Competent Authority for the manufacturer's place of business (Clause 5.1.4)
- Content: Trend Report (Clause 5.1.4 & Annex 7)

Trend Reports

- Report a significant increase in the rate of:
  - Already reportable incidents
  - Incidents that are usually exempt from reporting
  - Events that are usually not reported

- Report regardless of any agreed periodic summary reporting

Trending

- The implicit assumption is that the manufacturer knows the rate of incidents and events that are usually not reportable

- The GHTF guidance recommends:
  - Calculate rates for established time intervals
  - Establish a baseline rate, I_B
  - Establish a threshold rate, I_T

- Report if
  - The rate for a period exceeds the threshold
  - There is a continuous increase in the rate over an established number of periods

- Collect and analyze the data using EN ISO 13485:2016 Clause 8.4 Analysis of Data

Content

- The Trend Report form is in Annex 7

- Some information on the form is:
  - Date the trend was identified
  - Descriptive narrative of the trend
  - Time period of trend analysis
  - Established trigger level

- The form also includes information on the investigation, remedial action, corrective action, preventive action, and Field Safety Corrective Action

QUESTIONS