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Life Science, Pharma, Biotech & Med Dev

Growing Need for Clinical Data

Device PMCF plans and Registries

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About Your Presenter – Joy Frestedt

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Frestedt Incorporated named ***Best for Biotechnology Clinical Research 2016 – Minnesota*** in the 2016 Healthcare & Pharmaceutical Awards by the GHP Magazine

- President and CEO of **Frestedt Incorporated** (www.frestedt.com) and **Alimentix, the Minnesota Diet Research Center** (www.alimentix.com).
- Dr. Frestedt holds a PhD in Pathobiology from the University of Minnesota Medical School and a BA in genetics from Knox College. She is a member of SOCRA, RAPS, ASCO, AAPS and other organizations.
- Dr. Frestedt is among the "**100 Most Inspiring People in the Life Sciences Industry**" (PharmaVOICE, 2011) and the **top 25 "Industry Leaders"** (Minneapolis/St. Paul Business Journal, 2011). She authored two books: "**Warning Letters: 2016 Reference Guide**" with Barnett International and **"FDA Warning Letters about Food Products"** with Academic Press/Elsevier**.**
- Dr. Frestedt managed clinical trials, negotiated regulatory submissions and updated quality systems for over 35 years in health care, pharmaceutical, medical device and food industries including the University of Minnesota Medical Center, Orphan Medical, Johnson and Johnson, Astra Zeneca, CNS Therapeutics, Mayo Clinical Trial Services, Medtronic, AMS, etc.

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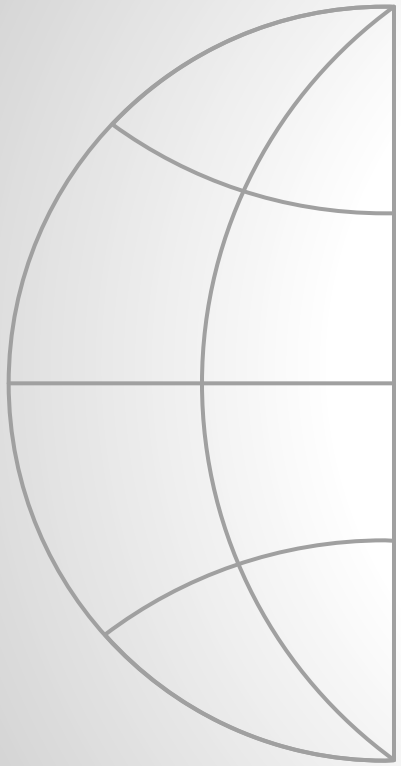
Overview

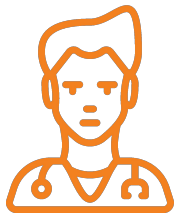
- Post Market Clinical Follow Up (PMCF) studies are a critical component of the clinical evidence required to comply with the European regulations (esp. the new Medical Device Regulation 2017/745, MDR and *In Vitro* Diagnostic Regulation 2017/746, IVDR going into effect in 2020).
- As Clinical Evidence Reports (CERs) for Medical Devices and Performance Evaluation Reports (PERs) for *In Vitro* Diagnostic Devices encounter more scrutiny by Notified Bodies (NBs), the gaps surrounding past PMCF work are becoming more evident.
- "Passive" collection of adverse events, complaints and other experience reports may not be sufficient any longer to demonstrate conformity to the Essential Requirements today or to the future MDR and IVDR.

This short 30-minute discussion will review emerging needs in this era of **pre-MDR business risk evaluations.**

Learner Objectives

- Clearly define PMCF/Registry needs for CERs
- Apply CER gaps in safety and performance to PMCF/Registry designs
- Differentiate adequate PMCF plans from less than adequate PMCF plans
- Discuss alternate methods to get clinical data
  - ✓ not necessarily a Clinical Trial





Agenda/Content

- ✓ Medical Device Regulations and Definitions
  - PMS, RMR, CER← clinical data →**PMCF**
- ✓ CER gaps in safety and performance
  - PMCF & registry designs
- ✓ Is PMCF plan adequate?
- ✓ Alternatives to PMCF trial?

MDR EU 2017/745 (05APR2017)

- Devices must conform to ***new*** Medical Device Regulation in 2020
- Experiences using devices must be “taken into account”
- Article 32: “…to be in conformity with the requirements of this regulation… all manufacturers should have a **quality management system** and a **post-market surveillance system** in place which should be proportionate to the risk class and the type of the device in question.”
- Article 33: “The **risk management system** should be carefully aligned with and reflected in the clinical evaluation for the device, including the **clinical risks to be addressed as part of clinical investigations, clinical evaluation and post-market clinical follow up**. The risk management and clinical evaluation processes should be inter-dependent and should be regularly updated.”

Confusing Terminology?

- Do not confuse traditional terms
  - ✓ **QMS** (to improve quality)
  - ✓ **RMR** (to manage design, process, use and other risks)
  - ✓ **PMSR** (to evaluate surveillance/experience data)
  - ✓ **CER** (to evaluate all clinical data in one place)
- **With PMCF (to update CER & ensure compliance)**

QMS=Quality Management System
RMR=Risk Management Report
PMSR=Post Market Surveillance Report
CER= Clinical Evaluation Report
PMCF=Post-Market Clinical Follow-Up

QMS Requirements

"(9) Manufacturers of devices, other than investigational devices, shall **establish, document, implement, maintain, keep up to date and continually improve a quality management system that shall ensure compliance with this regulation in the most effective manner and in a manner that is proportionate to the risk class and the type of device."**

"(74) Manufacturers should play an **active** role during the post-market phase by systematically and actively gathering information from post-market experience with their devices in order to update their technical documentation and cooperate with the national competent authorities in charge of vigilance and market surveillance activities. To this end**, manufacturers should establish a comprehensive post-market surveillance system, set up under their quality system,** and based on a post-market surveillance plan…**"**

What is a PMS Plan?

- “(74)…Relevant data and information gathered through post-market surveillance as well as lessons learned from any implemented preventive and/or corrective actions should be used to update and relevant part of the technical documentation, such as those related to risk assessment and clinical evaluation and should also serve the purpose of transparency.”

PMS Plan Purpose

- Record serious incidents (e.g., PSURs, field safety corrective actions)
- Record non-serious incidents and undesireable side-effects
- Report Trends
- Detail literature, database and/or registry data
- Document complaints/feedback from users, distributers, importers
- Record information about similar medial devices (public domain)

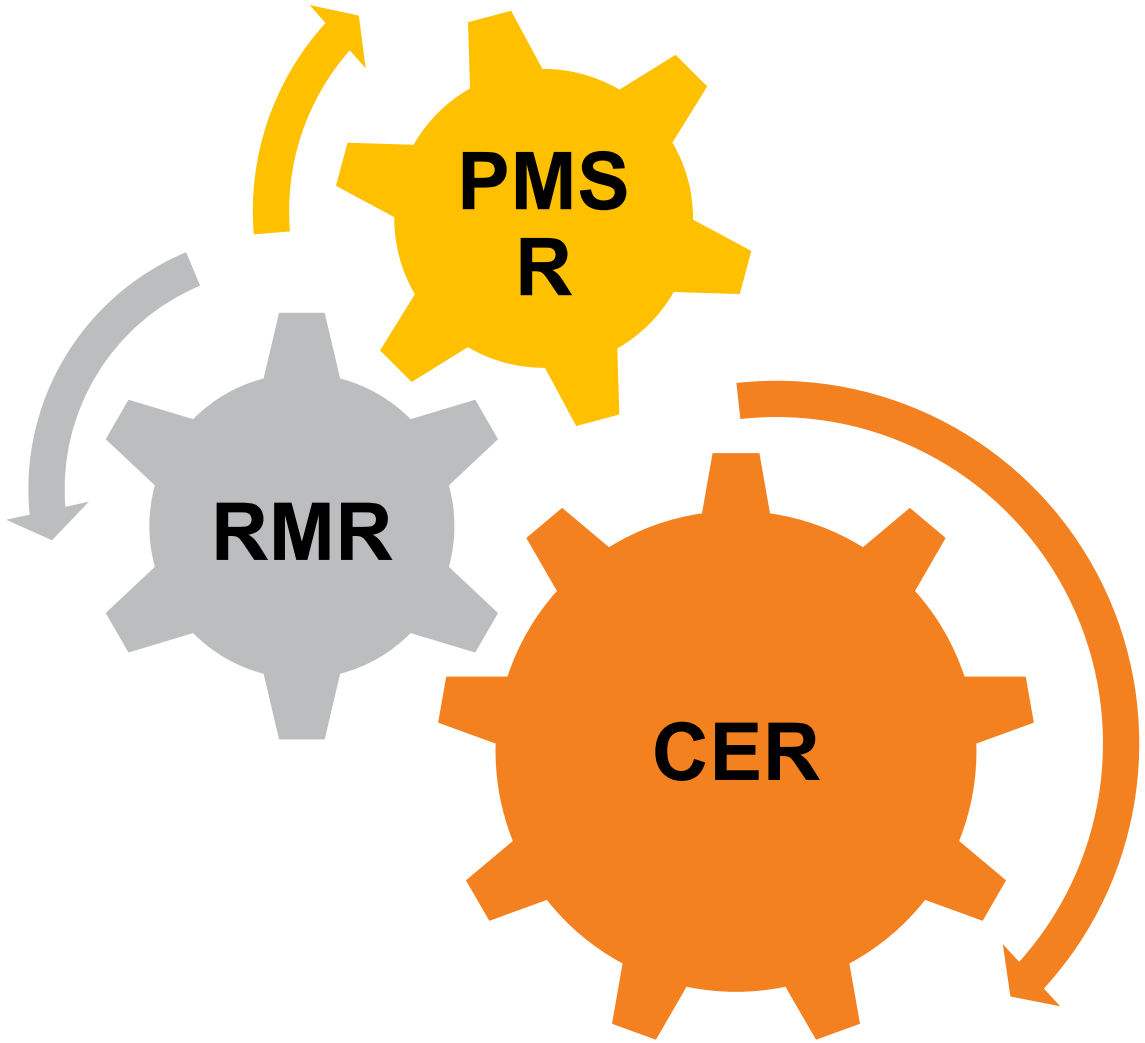
Clinical Evaluation Plan (CEP) Contents

- First, the CER needs a **Clinical Evaluation Plan (CEP)** including
  - ✓ Safety and performance data
  - ✓ Intended use
  - ✓ Target groups, indications, contraindications
  - ✓ Device description including benefits/outcomes
  - ✓ Specifications about methods to evaluate safety and to determine residual risks and side-effects
  - ✓ Specific parameters (based on state of the art) to evaluate acceptability of benefit/risk ratio for the indicated uses and purposes
  - ✓ Benefit-risk details about how to address any pharmaceutical, non-viable animal or human tissues
  - ✓ Clinical development plan including history, milestones and potential acceptance criteria
- **Sufficient clinical data are required** (evaluation "shall be thorough and objective" and must include favorable and unfavorable data and "shall be proportionate and appropriate to the nature, classification, intended purpose and risks of the device… as well as to the manufacturer's claims)

If not "sufficient," a PMCF clinical trial may be required…

Processes should be inter-dependent; updated regularly

RMR=Risk Management Report
PMSR=Post Market Surveillance Report
CER= Clinical Evaluation Report
PMCF=Post-Market Clinical Follow-Up



PMCF is a "continuous process that updates the clinical evaluation"

Clinical Trials | **Uses & Experiences** | **Literature**

Manufacturer "shall **proactively** collect and evaluate clinical data" from device uses as intended

Post-Market Surveillance (PMS) vs. PMCF

- Post-market surveillance – "All activities carried out by **manufacturers** in cooperation with other economic operators to institute and keep up to date a **systematic procedure** to **proactively collect and review experience** gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions."

vs.

- Post-market clinical follow-up – "…a **continuous process** that **updates the clinical evaluation**…and shall be addressed in the manufacturer's post-market clinical surveillance plan. When conducting PMCF, the manufacturer shall **proactively collect and evaluate clinical data** from the use in or on humans of a device which bears the CE marking and is placed on the market or put into service within its **intended purpose** as referred to in the relevant conformity assessment procedure, with the aim of **confirming the safety and performance throughout the expected lifetime of the device**, of ensuring the **continued acceptability of identified risks** and of **detecting emerging risks** on the basis of factual evidence."

Regulation (EU) 2017/745

Is a PMCF Plan Required?

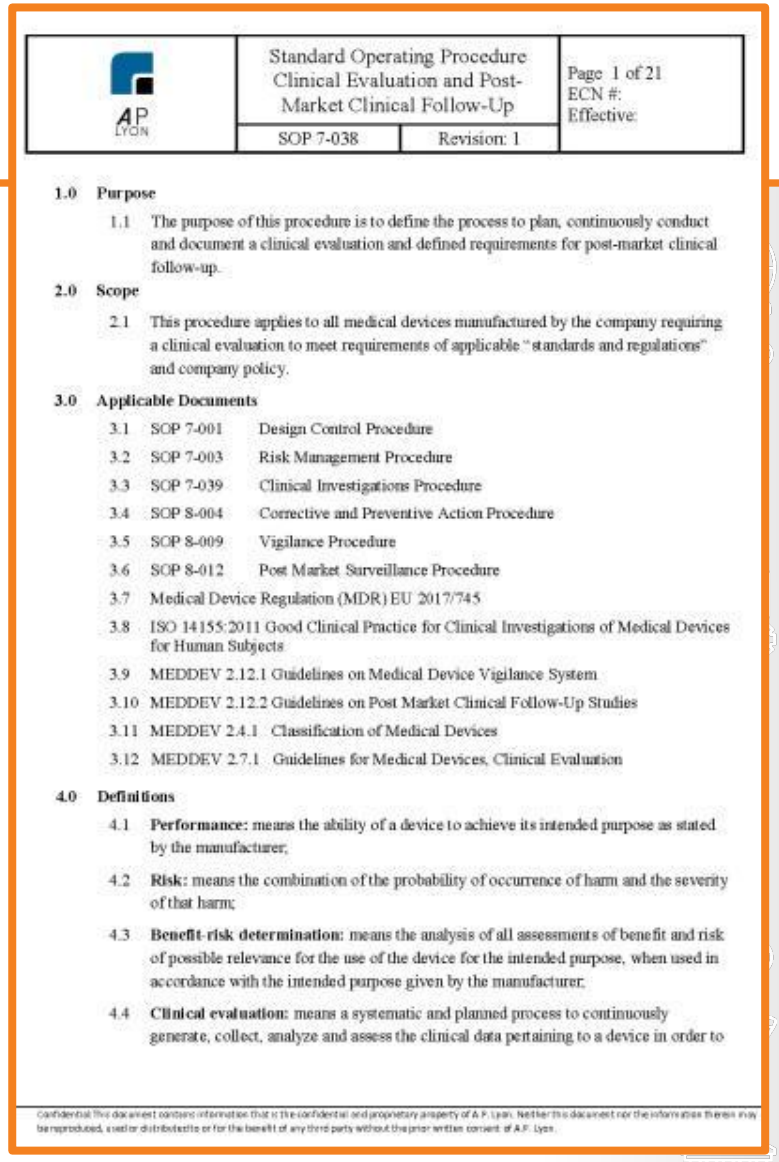
- YES (for all devices, regardless of class)
- "The manufacturer shall analyse the findings of the **PMCF** and document the results in a **PMCF** evaluation report… part of the [CER]… and the technical documentation."
- **PMCF** evaluation report conclusions "shall be taken into account" for the CER and RMR.
- "If… the need for preventive and/or corrective measures has been identified, the manufacturer shall implement them."
- In certain situations, **PMCF** maybe in a form other than a clinical trial

PMCF Plan may need to include "post market studies to demonstrate the safety and performance of the device."

PMCF Plan Purposes

- To document "procedures for **proactively** collecting and evaluating **clinical** data"
  - ✓ Confirm safety and performance during device lifetime
  - ✓ Identify and monitor side-effects and contraindications
  - ✓ Identify and analyze facts/evidence about emerging risks
  - ✓ Evaluate acceptability of benefit-risk ratio
  - ✓ Identify systematic misuse or off-label use and verify intended purpose is correct

If CER does not have sufficient clinical data (trials, literature experiences); the PMCF plan should explicitly seek the needed data to ensure the clinical data analysis is sufficient.



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Standard Operating Procedure
Clinical Evaluation and Post-Market Clinical Follow-Up

SOP 7-038 | Revision: 1

Page 1 of 21
ECN #:
Effective:

1.0 Purpose

1.1 The purpose of this procedure is to define the process to plan, continuously conduct and document a clinical evaluation and defined requirements for post-market clinical follow-up.

2.0 Scope

2.1 This procedure applies to all medical devices manufactured by the company requiring a clinical evaluation to meet requirements of applicable "standards and regulations" and company policy.

3.0 Applicable Documents

3.1 SOP 7-001 Design Control Procedure
3.2 SOP 7-003 Risk Management Procedure
3.3 SOP 7-039 Clinical Investigations Procedure
3.4 SOP 8-004 Corrective and Preventive Action Procedure
3.5 SOP 8-009 Vigilance Procedure
3.6 SOP 8-012 Post Market Surveillance Procedure
3.7 Medical Device Regulation (MDR) EU 2017/745
3.8 ISO 14155:2011 Good Clinical Practice for Clinical Investigations of Medical Devices for Human Subjects
3.9 MEDDEV 2.12.1 Guidelines on Medical Device Vigilance System
3.10 MEDDEV 2.12.2 Guidelines on Post Market Clinical Follow-Up Studies
3.11 MEDDEV 2.4.1 Classification of Medical Devices
3.12 MEDDEV 2.7.1 Guidelines for Medical Devices, Clinical Evaluation

4.0 Definitions

4.1 **Performance:** means the ability of a device to achieve its intended purpose as stated by the manufacturer;

4.2 **Risk:** means the combination of the probability of occurrence of harm and the severity of that harm;

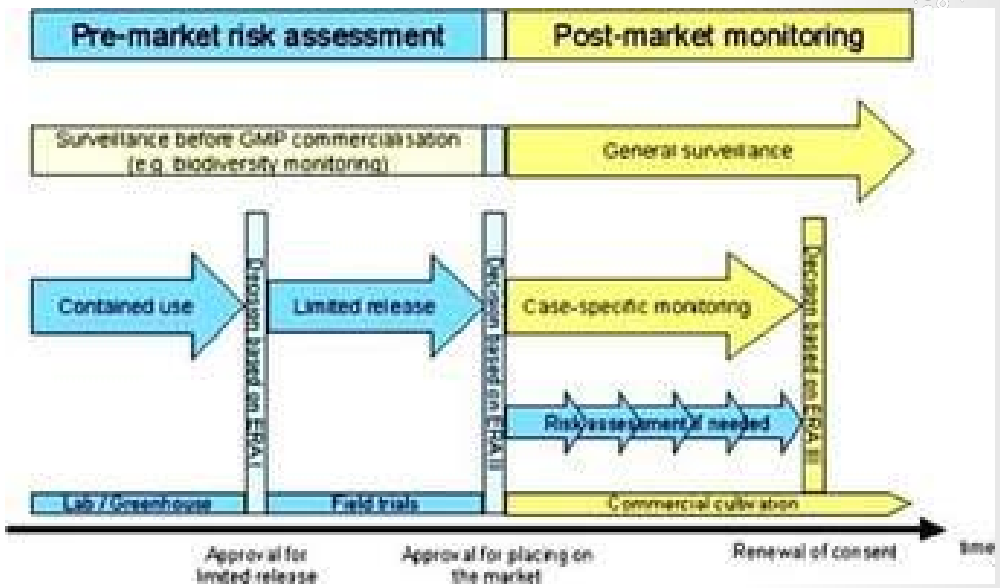
4.3 **Benefit-risk determination:** means the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer;

4.4 **Clinical evaluation:** means a systematic and planned process to continuously generate, collect, analyze and assess the clinical data pertaining to a device in order to

https://www.aplyon.com/store/p92/clinical-evaluation-procedures?gclid=CjwKCAiAoqXQBRA8EiwAIIOWsqVbhuwx44BydkyS9HBPW6g7Ko1EqJGWdPEGQmeMsUpdFV1o-zkxVRoCHHgQAvD_BwE

PMS Plan Contents

- The plan shall describe a proactive and systematic process (methods and protocols) to:
  - Collect and assess data
  - Allow a correct characterization of device performance
  - Compare to similar devices on the market.
  - Define suitable indicators and threshold values for benefit-risk analyses
  - Effective and appropriate method to evaluate complaints and market experiences in the field
  - Analyze trends (esp. any increase in frequency or severity)
  - Communicate with competent authorities, notified bodies, etc.



http://www.fao.org/docrep/meeting/008/y5871e/y5871e0n.htm

PMCF Plan Contents

- General methods and procedures
  - ✓ e.g., to gather users clinical experiences, feedback, literature reviews, etc.
- Specific methods and procedures
  - ✓ e.g., to evaluate suitable registers or PMCF studies
- Rationale to defend appropriateness of methods and procedures
- References to CER and RMR
- Specific **PMCF** objectives
- Evaluation of equivalent / similar device clinical data
- Reference to specifications, standards and **PMCF** guidance
- Timeline for **PMCF** data analysis and reporting

PMCF Topics of Consideration

- Innovation (design, materials, technology, principles of operation)
- New approved indication or claim
- Increased risk classification
- Increased risk in anatomical location
- Severity of disease
- Treatment challenges
- Ability to generalize clinical investigation results in question

- Unanswered questions involving long-term safety and performance:
  - ✓ Results from PMS activities
  - ✓ Newly identified unstudied population
  - ✓ Discrepancy in premarket follow-up time scales and life expectancy of product
  - ✓ Risks identified for similar devices
  - ✓ Sensitivity of target population
  - ✓ Interaction with other medical products/treatments
  - ✓ Training issues
- New safety or performance issues

GHTF/SG5/N4:2010

PMCF Integration

- **PMCF** must be accounted for in:
  - ✓ QMS
  - ✓ PMS Plan
  - ✓ Periodic Safety Update Report (PSUR)
  - ✓ **PMCF** Plan & Evaluation Report
  - ✓ Product Verification & Validation

PMCF Plan Objectives

The **PMCF** plan shall specify methods and procedures for proactively collecting and evaluating clinical data aiming to:

- Confirm safety and performance of device throughout its expected lifetime
- Identify previously unknown side-effects
- Monitor identified side-effects and contraindications
- Identify and analyz emergent risks on basis of factual evidence
- Ensure continued acceptability of benefit-risk ratio
- Identify possible systematic misuse or off-label use of device, with a view to verify intended purpose is correct

Regulation (EU) 2017/745 Part B

What needs to be included in a PMCF plan?

At a minimum, the **PMCF** plan must include:

- General methods and procedures of **PMCF** to be applied
  - ✓ Feedback from users
  - ✓ Screening of scientific literature
  - ✓ Collect and review of clinical data
  - ✓ Screening of other clinical data sources
- Specific methods and procedures of **PMCF** to be applied
  - ✓ Evaluation of registers
  - ✓ Evaluation of **PMCF** studies
- Rationale for appropriate general / specific methods and procedures

Regulation (EU) 2017/745 Part B

What else needs to be included in a PMCF plan?

- Reference to relevant CER parts
- Specific objectives to be addressed
- Evaluation of clinical data relating to equivalent or similar devices
- Reference to any relevant clinical standards, harmonized standards and guidance documents used
- Detailed and justified time schedule for PMCF activities
  - ✓ Analysis of data
  - ✓ Reporting
  - ✓ Next report

Regulation (EU) 2017/745 Part B

PMCF Evaluation Report

- Document **PMCF** results and findings
- Should be present in the CER and technical documentation
- If the **PMCF Report** identifies need for corrective or preventive action, the manufacturer shall implement those actions.

Adequate PMCF

- Proactive collects and evaluates clinical data when device used as intended
- Confirms the safety and performance throughout the expected device lifetime
- Ensures risks are acceptable when balanced against the benefits
- Identifies and monitors side-effects and contraindications
- Detects emerging risks
- Identifies misuse or off-label uses and verifies intended use is correct
- Data are based on factual evidence
- Method follows the PMCF plan

Inadequate PMCF

- **Passive** collection and evaluation of clinical data when device used as intended
- Level of clinical evidence is "**not sufficient** or otherwise gives rise to **serious concerns** about the benefit-risk determination" or consistency of the data to support the indications/intended uses

- If the clinical evidence is not sufficient, the Notified Body shall:
  - ✓ restrict the intended purpose to "certain groups of patients" or "medical indications"
  - ✓ Limit the duration of the valid certificate
  - ✓ Require specific PMCF studies
  - ✓ Change the instructions for use or summary of safety and performance
  - ✓ Other restrictions

Alternative Collection of Clinical Data

- Registry Study
- Post Card data collection
- Patient Information Form
- Physician Advisory Board Information
- Retrospective data review
- “Real World Evidence”
- Feedback from users

Remember: regulations, ethics, GCP, HIPAA and human subjects protections still apply!

Initial Steps for Planning a Registry

- Document the purpose
- Explain how the registry is needed and will meet the purpose
- Identify key stakeholders and assess feasibility
- Define scope, rigor and who will help on the "registry team"
- Specify the data set, patient outcomes, target population
- Develop plan/protocol
- Critically evaluate progress!

Registry Checklist

POPULATION: new initiators or recipients of treatment
TREATMENT: adequate detail recorded
COMPARATORS: concurrent
OUTCOMES: adequate detail; objective measures; measured similarly; validated or adjudicated
COVARIATES: recorded; accounted for in analysis
BIAS: sensitivity analysis; time bias

REF: Registries for Evaluating Patient outcomes: A User's Guide [Internet], 3rd Edition (2014)
https://www.ncbi.nlm.nih.gov/books/NBK208631/

Basic Registry Designs

- Cohort (group of patients followed over time, e.g., to see if they live longer)
- Case-control (match patients with/without a feature, e.g., to see if the feature affected survival)
- Case-series (a number of patients in order, e.g., to evaluate adverse events)
- Case study (an individual patient, e.g., to observe features of this one patient)

Poor or changing registry design or purpose = poor results

Whether using a REGISTRY or not,
collection of reliable CLINICAL DATA is required for PMCF

Wrap Up and Review: Learner Objectives

- Clearly Define PMCF/Registry needs for CERs
- Apply CER gaps in safety and performance to PMCF/Registry designs
- Differentiate adequate PMCF plans from less than adequate PMCF plans
- Discuss alternate methods to get clinical data

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