PCCP Project: Guidance Review

Marketing Submission Recommendations for a **P**redetermined **C**hange **C**ontrol **P**lan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions

Summary – PIcc

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BACKGROUND

Sec. 3308 of the Consolidated Appropriations Act 2023 states that subsequent guidance defining the approach to regulate predetermined change control plans.

- This is the draft guidance
- **Document issued on April 3, 2023**
- comments and suggestions regarding this draft document within 90 days
- Comment period is open until Summer

Contains Nonbinding Recommendations

Draft – Not for Implementation

Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on April 3, 2023.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact digitalhealth@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact ocod@fda.hhs.gov. For questions about this document regarding CDER-regulated products, contact druginfo@fda.hhs.gov. For questions about this document regarding combination products, contact the Office of Combination Products at combination@fda.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Office of Combination Products in the Office of the Commissioner

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Preface

Additional Copies

CDRH

Additional copies are available from the Internet. You may also send an email request to CDRH-Guidance@fda.hhs.gov to receive a copy of the draft guidance. Please include the document number GUI00020049 and complete title of the guidance in the request.

CBER

Additional copies are available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Room 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, by email, ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

CDER

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TOTAL OF 8 SECTIONS AND 2 APPENDICES

I. Introduction
II. Background
III. Scope
IV. Definitions: (1) Software Functions (2) Data sets (3) PCCP
V. Policy for PCCP: Components, Establishing, Identifying, Utilizing, Modifying
VI. Description of Modifications: goals, content, types
VII. Modification Protocol: goals, content, traceability (descr. & mod prot)
VIII. Impact assessment

I. INTRODUCTION

- ML-enabled technologies have the potential to transform healthcare
- subset of AI known as machine learning (ML) – henceforth referred to as *machine learning-enabled device software functions* or ML-DSFs
- Examples include
  - earlier disease detection and diagnosis
  - development of personalized diagnostics and therapeutics
  - development of assistive functions to improve the use of devices
- The goal of improving user and patient experience.
- **Validation:** "Validation means confirmation by examination and **provision of objective evidence** that the particular **requirements for a specific intended use** can be **consistently** fulfilled." 21 CFR 820.3(z); also section IV. for more information on definitions used for the purposes of this guidance.

II. Background

- Many components that led to this guidance
- Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback
- International Medical Device Regulators Forum's risk categorization principles
- Digital Health Software Precertification (Pre-Cert) Pilot Program
- Public Workshop on the "Evolving Role of Artificial Intelligence in Radiological Imaging"
- Patient Engagement Advisory Committee meeting on "Artificial Intelligence and Machine Learning in Medical Devices
- Public Workshop on "Transparency of Artificial Intelligence/Machine Learning-enabled Medical Devices"
- Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device Action Plan
- https://www.whitehouse.gov/ostp/ai-bill-of-rights/
- FDA may require that a **PCCP** include labeling for safe and effective use of a device as such device changes pursuant to such plan, notification requirements if the device does not function as intended pursuant to such plan, and performance requirements for changes made under the plan. Sections 515C(a)(3) and (b)(3) of the FD&C Act

FDA's Collaborative Patient-Centered Approach to AI/ML-Enabled Devices

Published AI/ML-SaMD Discussion Paper

2019

First joined Collaborative Community related to AI/ML

Evolving Role of AI in Radiological Imaging

Public Workshop on AI/ML in Radiological Imaging

2020

PEAC Mtg on Patient Trust in AI/ML Devices

Published AI/ML Medical Device Software Action Plan

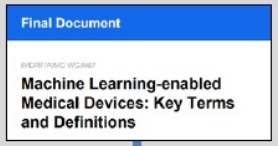
2021

Posted List of Currently Marketed AI/ML Devices

Transparency of AI/ML-Enabled Medical Devices

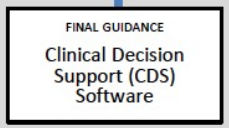
Public Workshop on Transparency of AI/ML Devices

Published GMLP Guiding Principles



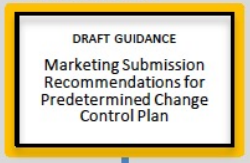
2022

Contributed to IMDRF's Key Terms and Definitions



Published Final Guidance: Clinical Decision Support

AI/ML Guidance



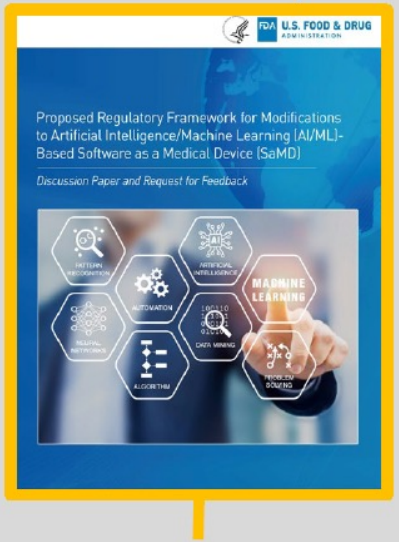
2023

We're working collaboratively with stakeholders to build a proactive, patient-centered approach to AI/ML-enabled devices that promotes health equity.

FDA's Collaborative Patient-Centered Approach to AI/ML-Enabled Devices

2019

Discussion Paper



Proposed regulatory framework for modifications to AI/ML-enabled medical device software to assure their safety and effectiveness, including **pre-specification of software changes to enable rapid improvement of software products**

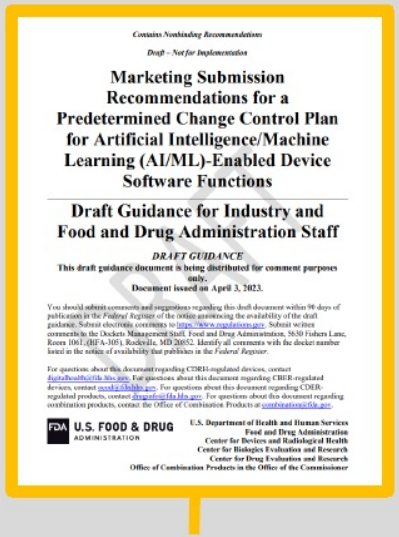
2021

Action Plan

Holistic, patient-centered strategic approach to AI/ML-enabled devices that promotes health equity, including aims to **update the proposed regulatory framework** and **foster a patient-centered approach, including transparency to users**

2023

Draft Guidance



Proposed, least burdensome approach to support safe, iterative improvement through modifications to an AI/ML-enabled device

III. Scope

- *Machine learning-enabled device software functions* or **ML-DSFs**
  - ML can allow software to learn through data, without being explicitly programmed, to perform a task.
  - One of the greatest potential benefits of ML resides in the ability to improve ML model performance through iterative modifications, including by learning from real-world data.
- Scope:
  ML-DSF that the manufacturer intends to modify over time.
  - **Automatic** modifications to the ML model
    - modifications are implemented automatically by software
  - **Manual** modification to the ML model
    - steps require human input, action, review, and/or decision-making.

SCOPE CONT'D

- approach that would often be least burdensome
- support the ability to modify an ML-DSF while continuing to provide a reasonable assurance of safety and effectiveness across relevant patient populations
- information to be included in the PCCP in a marketing submission
- By including a PCCP in a marketing submission, manufacturers can proactively pre-specify and seek premarket authorization
- Generally applicable to "combination products"
  - drug-device and biologic-device etc.

IV. Definition: Software & Data Sets

- Software function
  - **Device Software Function (DSF):** A software function that meets the device definition in section 201(h) of the FD&C Act. As discussed in other FDA Guidances, the term "function" is a distinct purpose of the product, which could be the intended use or a subset of the intended use of the product.
  - **Machine Learning-Enabled Device Software Function (ML-DSF):** A device software function that implements an ML model trained with ML techniques.

- Data sets
  - Training Data = to build a model
  - Tuning Data = evaluate + explore (do ***not*** **use** the word ***validation***)
  - Testing Data = independent, provide data to establish a reasonable assurance of safety and effectiveness

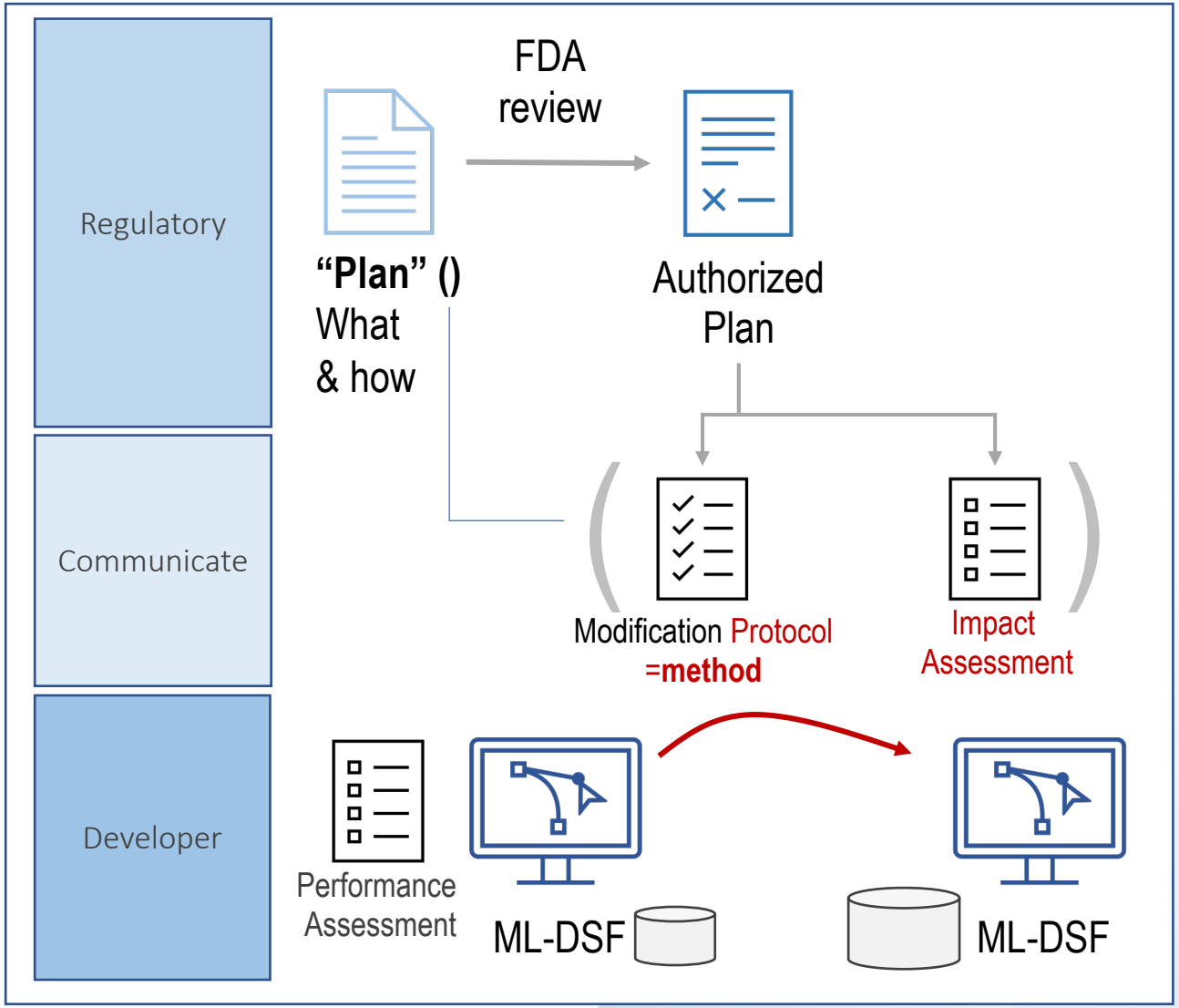
Term Mapping

2019 Discussion Paper		Current Draft Guidance
Predetermined Change Control Plan	→	Predetermined Change Control Plan
SaMD Pre-Specifications	→	Description of Modifications
Algorithm Change Protocol	→	Modification Protocol
Impact	→	Impact Assessment

SaMD = Software as a Medical Device

IV. Definition: PCCP

- **PCCPlan** = what changes and how assessed
- **Authorized PCCP** = Plan has been reviewed = technological characteristic of the authorized device.
- Modification Protocol = method that will be followed when:
  - Developing
  - Validating
  - Implementing modifications delineated in the "Description of Modifications"
- Impact Assessment = documentation of the assessment of risks and benefits of implementing the proposed PCCP



V. Policy

- authorized PCCP specifies planned modifications that, if not included in a PCCP, could otherwise require a new marketing submission
- Contains: “range of FDA-authorized specifications”
- Deviations from the authorized PCCP reviewed in the marketing submission could significantly affect the safety or effectiveness
- In such a circumstance, distribution of the ML-DSF without submitting a new marketing submission would constitute adulteration and misbranding … etc.

V. A) Components of a PCCP

- Exist as part of the PCCP
- Exist in tandem
  - Description of Modifications (DoM)
  - Modification Protocol (MP)
  - Impact Assessment (IA)

V. B) ESTABLISHING A PCCP

- established through
  - the 510(k) pathway,
  - De Novo pathway,
  - PMA pathway, as appropriate
- Existing devices must submit required documentation
- Q-submission encouraged

V. c) Identifying a PCCP in a submission

- standalone section within the marketing submission
- prominently included and discussed in the cover letter
- table of contents as “Predetermined Change Control Plan.”
- For ML-DSFs with an authorized PCCP, the labeling should explain that the device incorporates machine learning and has a PCCP so that users are aware that the device may require the user to perform software updates, and that such software updates may modify the device’s performance, inputs, or use.
- Should be described in the summary
- Details of the PCCP should be included in sufficient detail in the public-facing documents to support transparency to users of FDA’s determination of substantial equivalence or reasonable assurance of safety and effectiveness for the device and its range of FDA-authorized specifications.

V. D) UTILIZING OF A PCCP

- Process for implementing a modification
- The appropriate marketing submission could request authorization for
  1. a device modification effected through a change to the authorized PCCP (see Section V.E.);
     or
  2. a device modification not implemented through a PCCP;
     or
  3. 3) both.

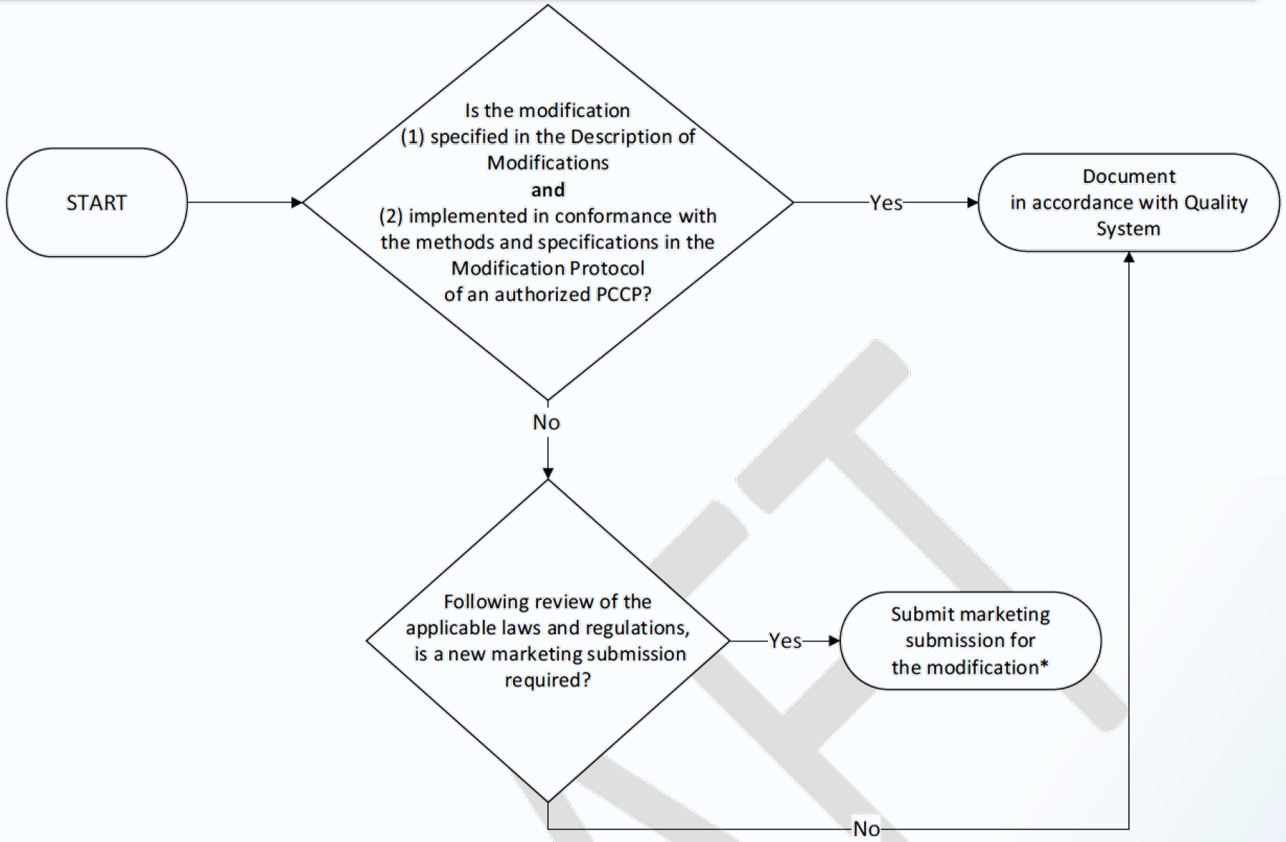


Figure 1: Implementing a Modification to a Device with an Authorized PCCP

V. E) MODIFYING A PCCP

- FDA expects that the modified PCCP will need to be reviewed and established as part of the premarket review of the modified device because a **modification to the PCCP** will generally significantly affect the safety or effectiveness of the device
- For a manufacturer who would like to modify a PCCP for a previously authorized device with a PCCP, the marketing submission must include the appropriate marketing submission requirements for the device and the proposed PCCP

VI. Description of Modifications

- **A. Goals:** identifies the specific "range of FDA-authorized specifications"
- **B. Content**: Description of Modifications should clearly state if the planned modifications are
- **C. Types:**
  - (i) modifications related to quantitative measures of ML-DSF performance specifications;
  - (ii) modifications related to device inputs to the ML-DSF; and
  - (iii) limited modifications related to the device's use and performance (e.g., for use within a specific subpopulation).
- FDA intends to, among other considerations, take into account the benefit-risk profile of the specific device that is the subject of the PCCP, the specific modifications being proposed, and its experience applying this policy across different device types

VII. Modification Protocol cont'd

- **A. Goals:**
  - Identify the method
  - Ensure that the information will be generated by manufacturer
  - Ensure risks have been identified
  - being traceable and specific to the modifications

- 1) **data** management practices,
- 2) **re-training** practices,
- 3) **performance evaluation protocols**, and
- 4) **update procedures**, including communication and transparency to users and real-world monitoring plans

Elements of a Modification Protocol

(1) Data Management	(2) Re-Training	(3) Performance Evaluation	(4) Update Procedures
• Collection Protocols • Assurance of Data Quality • Reference Standard Determination • Sequestration of Data Sets	• Re-training Objectives and Focus • Re-training Implementation	• Triggers to Initiate Performance Evaluation • Assessment Metrics and Elements • Statistical Analysis Plans • Performance Targets • Additional Testing Needs	• Software Verification and Validation • Update Implementation (When/How) • Communication and Transparency to Users • Device Monitoring Plan

From Appendix A

VII. Modification Protocol cont'd

- **B. Content:**
- 1) **data management practices**
  - what they are,
  - why they are recommended
    - How to obtain and use training and testing data
    - Identifiable subpopulations will be adequately represented
    - How training and testing will be sequestered to prevent overfitting
    - How older data will be complemented or replaced
    - Reference standard is representative of the patient population
    - How the data management practices may reduce the potential to produce discriminatory outcomes
  - What manufacturers should include in a submission

VII. Modification Protocol cont'd

- **B. Content:**
- 2) **re-training** practices,
  - what they are
    - Describe the rationale (e.g., ML architecture modification in a neural network)
  - why they are recommended
    - typically provided in the "device description"
  - What manufacturers should include in a submission
    - E.g., data sequestration strategies

VII. Modification Protocol cont'd

- **B. Content:**
- 3) **performance evaluation** protocols, and
  - what they are
    - Performance evaluation methods should describe
    - plans for verification and validation of the entire device following ML-DSF modifications
    - **for each** individual modification
    - AND
    - **in aggregate** for all implemented modifications
  - why they are recommended
    - confirm that appropriate study designs, including performance metrics and statistical tests
  - What manufacturers should include in a submission
    - INFORMATION = APPENDIX A

VII. Modification Protocol cont'd

- **B. Content:**
- 4) **update procedures**
  - **what** they are
  - **why** they are recommended
    - How risks may be mitigated
    - How modifications will be communicated to users
    - How the device operation will remain reliable after update
    - How all stakeholders will be kept up-to-date
  - What manufacturers should **include in a submission**
    - Confirmation the verification and validation plan are the same
    - Description of how the software updates will be implemented
    - How legacy users will be affected
    - How modifications will be communicated

VII. Modification Protocol cont'd

- **C. Traceability Between the Description of Modifications** 754 **Section and the Modification Protocol Section**

Table 1. Example of Description of Modifications to Modification Protocol Traceability Table

Table 1: A traceability table can help to identify where each method supporting each modification may be found in the marketing submission.

	Modification Protocol Component			
Modification	Data management practices	Re-training practices	Performance evaluation	Update procedures
Modification #1	*Method A (see Section X.A)*	*Method D (see Section X.D)*	*Method G (see Section X.G)*	*Method J (see Section X.J)*
Modification #2	*Method A (see Section X.A)*	*Method E (see Section X.E)*	*Method H (see Section X.H)*	*Method J (see Section X.J)*
Modification #3	*Method B (see Section X.B)*	*Method F (see Section X.F)*	*Method I (see Section X.I)*	*Method J (see Section X.J)*

VIII. Impact Assessment

- Impact Assessment documentation in a marketing submission should discuss
  - how the individual modifications included in the PCCP
    - impact the ML-DSF
    - how they impact the overall functionality of the device,
    - how they impact other device software functions,
    - as well as device hardware.
- Link to Multiple Function of a Device

Impact Assessment

Documentation for an Impact Assessment provided to the Agency in a marketing submission containing a PCCP should:

1. Compare version of device with each modification implemented to version of device without any modifications implemented
2. Discuss benefits and risks of each individual modification
3. Discuss how activities proposed within Modification Protocol continue to reasonably ensure safety and effectiveness of device
4. Discuss how implementation of one modification impacts implementation of another
5. Discuss collective impact of implementing all modifications

APPENDIX A.
EXAMPLE ELEMENTS

d. Sequestration of test data sets

For the purposes of this guidance, sequestration of test data sets means that manufacturers do not have access to the test data set for the purpose of ML-DSF development.

1.d.1. What strategies will be employed at the outset of data collection to shield the test data set from the ML-DSF development?
1.d.2. What are the specific procedures to be followed so that the test data set remains sequestered during re-training?
1.d.3. If test data are planned to be used multiple times for performance evaluation, what measures are in place to prevent unwanted bias from being introduced through ML model manufacturers learning substantial information about the test data set and results?

(2) Re-Training

a. Re-training objectives and focus

2.a.1. How are the modifications presented in the Description of Modifications in the PCCP related to the planned re-training methods?
2.a.2. Which parts of the ML-DSF are planned to be modified (e.g., transfer learning, data pre-processing, data augmentation, only a certain set of coefficients, ML architecture and hyper-parameters, loss functions, optimization methods and criteria, types of ML model inputs and outputs), and what are the details of the planned modifications to the ML-DSF design? What is the specific rationale for the change to each part that is planned to be modified?
2.a.3. For each part of the ML-DSF that will be modified, is ML model re-training needed to achieve the modifications specified in the PCCP?

APPENDIX B.
ML-DSF SCENARIOS

Contains Nonbinding Recommendations

Draft – Not for Implementation

Post-Authorization Modification Scenario:

Modification Scenario 1: Modification related to quantitative measures of device performance, as specified in the PCCP, and implemented in accordance with the PCCP

In accordance with the Modification Protocol, imaging data were collected and used to re-train the ML model. The modified ML model was tested according to a specified test protocol in the Modification Protocol. The results demonstrated that the sensitivity and specificity for abnormality identification met statistical superiority pre-specifications. Labeling was updated in accordance with the modified device performance, and communication was provided to the device users. Because the device modification was specified in the PCCP, and because it was implemented in conformance with the PCCP, the device modification would not require a new marketing submission. The manufacturer should document the modification that was specified in the PCCP in accordance with their quality system.

Modification Scenario 2: Modification related to the device's use and performance that was not specified in the PCCP

The manufacturer used new images to re-train the ML model and would like to update their labeling to reflect improved performance in the same shoulder region in a subset of the pediatric patient population identified in the device's indications for use. However, the modification was not specified in the PCCP. Because this modification that was not included in the PCCP could significantly affect the safety or effectiveness of the device, a new marketing submission would be required.

To do

WEBSITE OVERVIEW = RESOURCE

DISCUSSION

COMMENT PERIOD

FOLLOW-UP MEETING

PROJECTS?

- METHOD STUDY DESIGN
- TOOLS & TEMPLATES
- WHAT WOULD YOU LIKE TO DO?

https://pathologyinnovationcc.org/projects/pccp-project