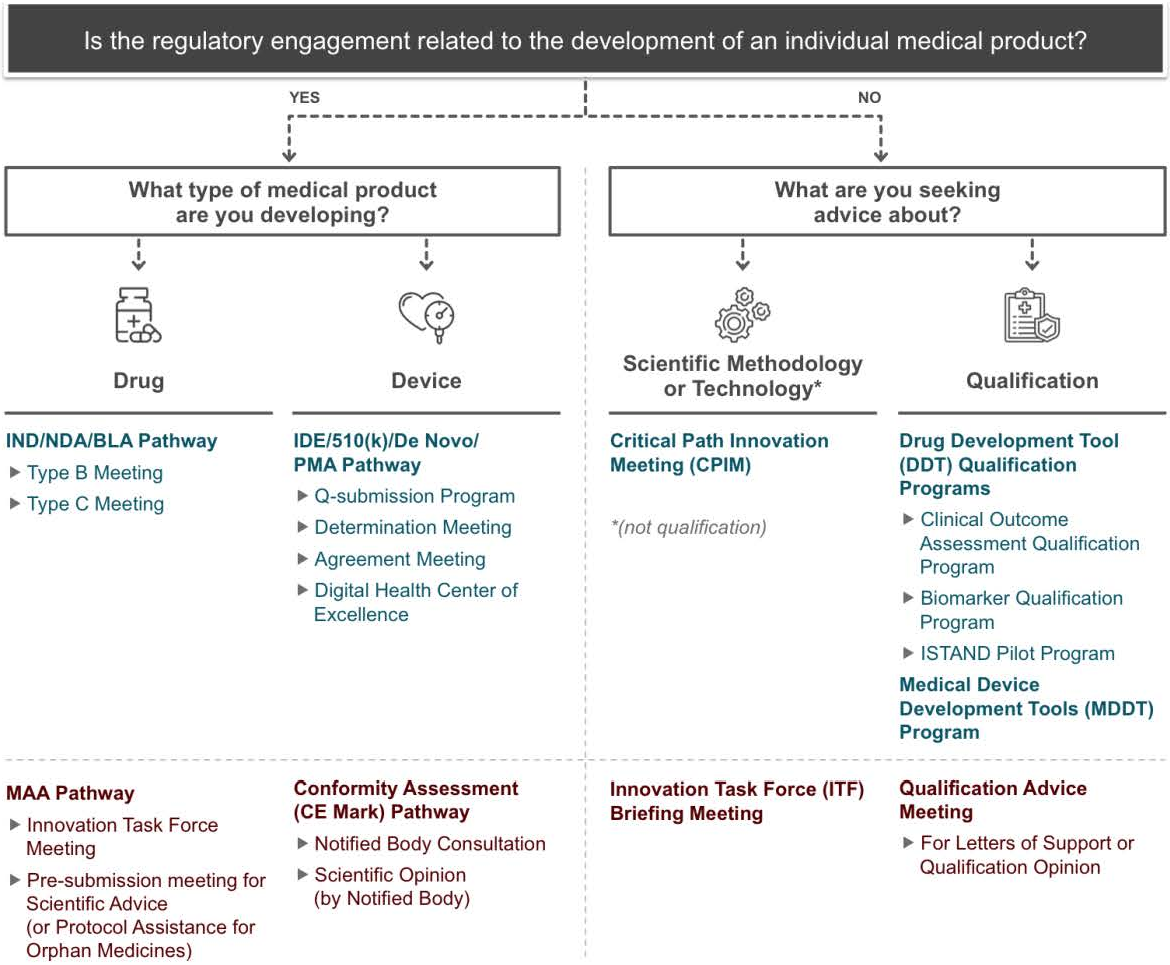
CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Regulatory Engagement Opportunities when Developing Digitally Derived Endpoints



Appendix: FDA Engagement Opportunity Overview

IND/NDA/BLA Pathways

Specific to individual drug development programs

- Type B Meeting

  Potential Topics: Endpoint development strategy. Formal, intended for general advice on a planned submission (and could be binding).

- Type C Meeting

  Potential Topics: Any topics not addressed in Type A (stalled product development) or Type B meetings; if concept of interest (COI) is acceptable; rationale for the context of use (COU), if DHT-measure is meaningful to patient; analytical and/or clinical validation results (including minimal clinically important difference [MCID]); risk evaluation and mitigation strategies; end of phase advice. Formal and could be binding.

IDE/510(k)/De Novo/PMA Pathway

Specific to individual medical device development programs for clearance or authorization of a medical device

- Q-submission Program

  Potential topics: can vary, such as advice on investigational plan/protocol, general advice prior to submission of an IDE, 510(k), De Novo, or PMA. Less formal interaction.

- Determination Meetings

  Potential Topics: determine the type of valid scientific evidence needed to demonstrate the device is effective for its intended use. Binding, specific to a single PMA program.

- Agreement Meetings

  Potential Topics: agree on key parameters of the investigational plan and protocol. Binding, open to PMA and 510(k) programs.

- Digital Health Center of Excellence

  For general digital health inquiries and advice on interpretation of digital health guidance documents and/or regulatory status of a digital health technology

Critical Path Innovation Meeting (CPIM)

General advice on methodology or technology to enhance drug development

Drug Development Tool (DDT) Qualification Programs

Program to qualify a tool that sponsors can use in the development and evaluation of drugs; applicable to different drugs or diseases

DDT programs include submission of a letter of intent (LOI), followed by a qualification plan (QP), and then a full qualification package (FQP)

Potential Topics:

- pre-LOI meetings available on a case-by-case basis to help submitters understand the qualification process and offer suggestions on ways to optimize their submissions.
- LOI: concept of interest, context of use, description of the measure, unmet need for the instrument.
- QP: qualitative evidence, qualitative study protocol, qualitative results, interview guides, quantitative (statistical) analysis plan.
- FQP: QP documents, qualitative study protocol, qualitative results, Interview guides, quantitative (statistical) analyses plan, results from quantitative analyses, datasets.

▶ COA Qualification Program

Program to qualify a COA instrument of a specified COI for use in studies in a specified COU.

▶ Biomarker Qualification Program

Program to qualify a biomarker instrument of a specified COI for use in studies in a specified COU.

▶ ISTAND Pilot Program

Program for DDTs that are out of scope for others DDT qualification programs but may still be beneficial for drug development.

Medical Device Development Tools (MDDT) Program

Program to qualify a tool that sponsors can use in the development and evaluation of medical devices; applicable to different devices or diseases

Potential Topics:

- Proposal Phase: feedback on evidence gathering plan.
- Qualification Phase: review of collected evidence.

Appendix: EMA Engagement Opportunity Overview

MAA Pathway

Procedural and regulatory advice before a marketing authorization.

- Pre-submission meeting for Scientific Advice (or Protocol Assistance for Orphan Medicines)

  Advice on best methods and study designs to generate robust evidence for a specific medicinal product in a clinical program.

  Potential Topics: Endpoint development strategy, if COI is acceptable, rationale for the COU, if DHT-measure is meaningful to patient, how the technology will provide clinically meaningful data; analytical and/or clinical validation results (including MCID); written advice, binding.

Conformity Assessment (CE Mark) Pathway

Demonstrate that a medical device meets legal requirements to ensure it is safe and performs as intended

- Notified Body Consultation

  If needed prior to CE Marking (EMA not involved).

  Potential Topics: general advice on medical device development and scientific evidence necessary to demonstrate safety and performance.

- Scientific Opinion

  Obtained by the Notified Body on behalf of the applicant for some medical devices (i.e. when devices are used with drugs).

  Potential Topics: advice on scientific evidence necessary to demonstrate safety and performance for significant-risk devices.

Innovation Task Force (ITF) Briefing Meeting

General advice on methodology or technology to enhance drug development; not binding.

Qualification Advice Meeting

Advice on a methodology or technology to be used for pivotal trials (based on data from exploratory studies); applicable to different medicinal products or diseases.

Potential Topics: the methodology and its clinical usefulness, added benefits compared to traditional methods, whether the clinical measure taken with the technology is fit for the intended use in regulatory decision making (content validity, construct validity, reliability and sensitivity to change), generalizability and clinical applicability of the methodology.

Qualification Advice meeting may result in a **Letter of Support** (if further qualification is needed) and a **Qualification Opinion** may be sought (binding).

Interactions with Health Technology Assessment (HTA) bodies are out of scope of this document. HTA engagements may vary depending on the country.

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