EXCITE INTERNATIONAL

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Working Framework for Payers Advisory Committee

This document is developed to provide a framework for Payers Advisory Committee (PAC) members. While there is no intent to provide a consensus relating to a specific technology, this document provides high-level decision determinants that could guide PAC when providing advice to technology developers (companies). This is derived from a previous PAC document on evidence expectations by Payers and from Early Technology Reviews (ETR) to date. The current version is incomplete and awaits PAC input.

Section A provides background information for PAC members with information relating to evidence requirements by Payers and health professions while Section B provides specific information regarding PAC and its deliverables. It is intended that this living document will be continuously updated to provide a high-level approach acceptable to PAC members. ***It should be emphasized that PAC does not attempt to establish a consensus approach to coverage/reimbursement decision making, which falls under the strict purview of independent insurers. Neither does PAC advice necessarily imply subsequent positive coverage.***

SECTION A: Background

Evidence expectations of health professionals and Payers includes well-designed and statistically powered clinical trials that address comparative effectiveness based on outcomes, target populations and comparators relevant to their expectations. Too often, these expectations are only made known after clinical trials are conducted to satisfy regulatory requirements, when it is too late to address these expectations. The ecosystem in which the technology is expected to perform including its place in treatment pathways and whether it should be deployed as a substitute, adjunctive or additive technology to comparable technologies could affect clinical trial development and economic considerations. Tackling Payer and health professional expectations ***early*** in the technology development lifecycle could improve the likelihood of an expedited positive coverage determination and adoption.

The evidentiary pathway for regulated innovative medical devices (non-drug technologies) is primarily focused on satisfying regulatory requirements with the result that health professionals, Payer and patient expectations may not be met, despite a considerable investment in clinical trials. The dissociation between regulatory market authorization and coverage determination has financial consequences. For example, in 2010, the average cost for a pivotal trial to address 510(k) expectations was $24 million, and for a Class III medical device going through Premarket Approval (PMA), the cost was $94 million. [1] Embarking on the

[1] Makower J, Meer A, Denend L. FDA Impact on U.S. medical technology innovatIon: A Survey of Over 200 Medical Technology Companies • November 2010. liye.info-fda-impact-on-us-medical-technology-innovation-advamed-

regulatory pathway without considering the expectations of health professionals and Payers is potentially wasteful and may result in disappointment when it comes to coverage determination and professional guideline development/adoption.

In a cross-sectional study, only 99/218 (45%) of new devices in clinical trials ultimately received regulatory clearance or approval[2]. Even if FDA-approved, there is uncertainty regarding subsequent coverage.

Medical devices with 510(k) clearance are more likely to face coverage restrictions by CMS[3] which often adds conditions such as restricting coverage to patients with the most severe disease.[4] Moreover, widespread adoption beyond CMS coverage is hindered by the fact that CMS reimbursement does not guarantee adoption by private insurers.[5]

FDA provides early advice to companies through pre-submissions and further in-depth meetings to inform them of regulatory expectations. Likewise, early engagement with Payers and health professionals should also be provided to improve the efficiency of early evidence development.

Small and medium-sized enterprises (SMEs) with limited resources are most likely to prioritize satisfying regulatory expectations without understanding those of Payers and health professionals driven by (i) the urgency of getting their product to market with few insights of what that entails and (ii) the excellent guidance provided by FDA to satisfy regulatory expectations.

Even for small companies seeking an early off-ramp to be bought out early by larger strategic companies, failure to demonstrate a sound evidence-based approach to product development that meets downstream expectations of Payers and health professionals will compromise their success in this regard. This is because larger companies favor technologies that have been evaluated by appropriately-designed and statistically- validated clinical trials that focus on relevant comparators, outcomes and target populations.

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pr_368999ab224f4f6683be4ba59401485e.pdfFDA impact of U.S. medical technology innovation–A survey of over 200 medical technology companies. 2010; Aabed Meer, Lyn Denend

[2] Marcus H J, Payne C J, Hughes-Hallett A, Marcus A P, Yang G, Darzi A et al. Regulatory approval of new medical devices: cross sectional study. *BMJ* 2016; 353 :i2587 doi:10.1136/bmj.i2587

[3]

[4] Chambers JD, May KE, Neumann PJ. Medicare covers the majority of FDA-approved devices and Part B drugs, but restrictions and discrepancies remain. Health Aff (Millwood). 2013 Jun;32(6):1109-15

[5] Chambers JD, Chenoweth M, Thorat T and Neumann PJ. Private Payers Disagree with Medicare Over Medical Device Coverage About Half the Time. Health affairs 2015; 8: 1376–1382

EXCITE International: Early Technology Review (ETR) and Clinical Trials

EXCITE International (EXCITE), a non-profit organization, was incorporated as a multi-stakeholder initiative in 2016 to provide an opportunity for companies with impactful medical technologies to engage directly with Payers and health professionals ***early*** in technology development. This was to provide companies with insights into downstream expectations by Payers and health professionals to better-inform pre-market development and evaluation and in so-doing, increase the chances of a positive coverage determination following regulatory approval. This could also inform professional guideline development. Visit www.exciteinternational.com for further details.

The EXCITE approach consists of two components. The first is an Early Technology Review (ETR), which informs companies of health professional and Payer expectations and early expression of interest. This includes a perspective on appropriate target populations, comparators and thresholds, unintended consequences and helping appreciate changes in patient outcomes and/or health system efficiencies most likely to bring about change in practice and/or funding. The ETR also allows companies and stakeholders to understand more fully whether the technology addresses unmet needs, informs the company regarding further product development as appropriate and identifies potential facilitators and barriers to adoption. The ETR is supported by an evidence-based analysis of the technology and comparators.

The ETR provides an opportunity for companies to engage with Payers, health professionals and methodologists ("stakeholders") usually at the proof of concept stage but at any stage up to and including pivotal trial development. The ETR is informed by a robust objective evidence-based analysis building on the Population, Intervention, Comparator, and Outcomes (PICO) method, contextualized by health professionals and Payers. This emphasizes the importance of a well-formulated research question to guide an evidence review and provides clarity about the individual PICO components to establish the agreed-to basis for the evidence review. [6] This is followed by an analysis of systematic reviews and meta-analyses undertaken in the last five years, complemented by a systemic review of randomized controlled trials (RCT) undertaken from the date of last publication in the analysis.

The ETR is undertaken by a Panel, selected from the Payers Advisory Committee (PAC), the Scientific Collaboration, and health professionals relevant to the technology under consideration, all being bound by a non-disclosure agreement. Invited presentations provide additional information as appropriate. Regulatory perspectives are provided by the company at its discretion, reflecting their communication with regulatory authorities. The company participates in all Panel meetings to ensure transparency and to provide information related to the technology under reviews. The final ETR is reviewed by the full PAC and Scientific

[6] Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schunemann HJ: GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011, 64(4):395–400

Collaboration and is shared with the company at which point it becomes their intellectual property. While the company may share the content of the ETR at its discretion, it remains confidential to EXCITE and the panel. The ETR does not promote a specific product and reflects an objective, evidence-based approach.

The ETR forms a comprehensive platform on which to build a protocol for any subsequent clinical trial, working on the premise that clinical trials are the most important consideration for health professionals to consider using the technology and for Payers to consider payment and reimbursement. It is therefore imperative that these stakeholders are fully engaged in protocol development. Clinical trials based on the ETR are undertaken through a special relationship between EXCITE and the Harvard-associated Baim Institute of Clinical Research.

Basic considerations for an ETR Framework informed by an early evidence review are:

- Assessment of relevance, based on unmet need and potential impact in improving patient outcomes or health system efficiencies formulated by discussion between Payers and health professionals.
- Defining the appropriate target population to maximize patient outcomes, based on the company's initial perspective and contextualized by health professionals and Payers
- Identifying comparators relevant to health professionals and Payers. This allows health professionals and Payers to determine comparative effectiveness of the new technology against existing alternatives. Comparative effectiveness is essential when considering professional guideline development and coverage determinations.
- Advice regarding the most relevant outcomes that reflect an improvement in patient outcomes and/or health systems efficiencies.
- Advice on deployment as a replacement, sequential or adjunctive technology.
- An assessment of analytical and clinical validity and clinical utility for biomarkers and advice on whether these are sufficient to satisfy health professionals and Payers
- Safety issues including weighing risks and benefits and identifying unintended consequences.
- Regulatory requirements shared by the company to establish if these can be included in a broad- based clinical trial that can also address health professional and Payer expectations
- Health economic modeling to provide estimates of downstream events and costs avoided/ incurred, a cost-effective analysis and to determine which uncertainty is the most important to study in a clinical trial. This is optional but recommended if the intent is to enter the U.K., Canadian or European markets.
- High level advice on approaches to coverage determination in the U.S. with specific reference to the technology being reviewed. This includes a review of statutory requirements for CMS coverage as appropriate, advice on approaches to coverage determination using general and specific codes, and an approach to CMS national vs local coverage determinations.
- Positioning within defined clinical pathways contextualized for intended markets
- High level advice regarding proof of concept and pivotal trial design from the perspective of health professionals and Payers in particular.

The Framework is expanded according to the technology under consideration. Fundamental to the final Framework is a requirement that it strikes a balance between its constituent parts and, in particular, the need to balance between unmet needs and evidence generation.

Technologies include devices, diagnostics, molecular biological markers and digital health technologies.

To date, EXCITE has undertaken fifteen ETRs since the program began in 2017. Given the evolutionary nature of the ETR process, this initiative began cautiously and increased rapidly in 2022/23.

The EXCITE experience has demonstrated that early and direct involvement in technology development by Payers, health professionals and patients through an objective, evidence-based approach can be successfully achieved. This transformational approach could reduce the risk of adverse outcomes including unmet investment expectations and failure to secure a positive coverage determination and/or acceptance by health professional and patients.

SECTION B: PAC Involvement in EXCITE Evidence Development

1- Advice to Technology Developers

1.1. General Considerations Regarding PAC Involvement

The following factors guide Payer involvement in the EXCITE-mediated engagement with medical technology companies:

- Payer input into EXCITE processes are not representative of PAC member home organizations.
- Any advice provided through EXCITE has no bearing on final coverage decision making by any insurer, all of whom have independent policy-based decision-making processes which are not affected by any EXCITE process. Specifically:
    - Neither the selection of a candidate technology nor the endorsement of a study protocol will obligate any Insurer to adopt the technology under consideration.
    - Rejection by EXCITE International does not exclude future consideration by Insurers.
- Advice provided by PAC members must be available in the public domain and is based on experience gleaned from their workings at the senior evidence to policy interface
- All records of committee meetings are anonymized.
- Companies are not permitted to contact PAC members directly.
- All proceedings are strictly confidential.

- PAC members are indemnified for EXCITE-related work, as long as they comply with EXCITE expectations, and, in particular, maintaining confidentiality.**1.2. Overall PAC Advisory Functions**

PAC is one of several advisory groups to the EXCITE Board and has three functions:

- Early advice to companies on the relevance of a technology to Payers. This advice may be sought as early as the conceptual phase/prototype development, proof-of-concept stage to pivotal trial development and execution and occurs through PAC's contribution to the EXCITE ETR offering and clinical trial protocol development.

  In fulfilling its advisory functions, PAC is guided by two overarching principles. First, that the mission of EXCITE is to accelerate adoption of impactful technologies in order to improve the well-being of patients. Second, that the role of PAC is to provide Payer and health system perspectives early in the technology life cycle. Outcomes of importance are comparative effectiveness with respect to alternative technologies, the representativeness of populations, the relevance of pragmatic and real-world approaches, and the impact on population health and system efficiencies.

  These perspectives differ from those of regulators, which oversee the entry of technologies into the marketplace, underpinned by proof of safety and evidence that the technology performs according to the manufacturer's claims. Payers and health systems must choose from the marketplace in order to effectively and efficiently fulfill their commitment to the health of their beneficiary populations.

1.3. Advice on selecting technologies for evaluation by EXCITE, based on pre-defined criteria and processes.

When selecting a candidate technology, PAC considers the following:

- Potential to be an impactful innovation with a major effect on patient outcomes and/or health system efficiencies.
- Presence or absence of alternative interventions aimed at improving patient outcomes and/or health systems efficiencies
- Dimensions considered in judging the impact on patient outcomes include burden of disease (prevalence and severity), unmet need, and potential to improve access.
- The technology addresses an important challenge in the delivery of care to a population or an important challenge to the health system as a whole. Examples include reducing hospitalization, reducing invasiveness, or improving control of a chronic disease.
- With respect to orphan diseases, the severity and need may be sufficient, irrespective of disease prevalence and/or impact on the health system.

- Feasibility to implement with defined barriers and facilitators for adoption through consideration of design, coverage and payment that may affect the uptake of the technology and infrastructure and resource requirements for delivery.
- Potential deployment as an adjunct, replacement, or prompting obsolescence of the existing comparator.

1.4. Input into protocol development

Advice on protocol development is intended to ensure that the quality, design, and outcomes are consistent with the needs and expectations of Payers. The ETR is a platform on which to build a clinical trial protocol that meets the expectations of Payers and health professionals. This is achieved through the special relationship EXCITE has with the Harvard-associated Baim Institute of Clinical Research. PAC is asked to become further involved in protocol development to ensure that Payer perspectives are reflected in the final protocol.

2. Input into Evidence Development that Guides Coverage Determinations (Derived from existing PAC document)

Regulatory-approved medical technologies often fail to meet Payer expectations due to the evidence necessary to make a coverage decision. The reasons largely fall into two categories, these being, the relevance of the evidence (see2.1 Below) and the methodological quality and credibility of the evidence (see 2.2 below).

2.1 Relevance domains

Is the study population clearly defined and representative of the population for whom the technology is intended?

Some important elements of defining the population include diagnosis, disease severity, prior treatments, comorbidities, and demographic characteristics such as age and sex. The study population should be specifically stated in the protocol and generalizable to the patient populations for whom the technology will be used in clinical practice. However, there may be some differences across jurisdictions in the populations of interest due to differences in care pathways and patterns of care.

Does the technology as designed and used in the study represent the intervention that will be used in clinical practice?

Some important elements of defining the intervention technology include intensity, delivery, operators, setting, as well as pre-and post-procedural care. Refinements to a technology through clinical trial experience may be addressed by an adaptive design approach.

Is the comparator intervention appropriate and representative of existing alternative(s)? Is the comparator delivered effectively, with similar intensity, and by capable operators in the appropriate setting?

Choice of comparator also depends on whether the intervention technology is intended as an adjunct or a replacement to established care. In the case of a novel innovation for an unmet need, the comparator may be best supportive care. Natural history is a relevant comparator in the absence of supportive care, but there are few conditions for which there is no supportive care. Caution is merited with "usual care comparators" as usual care may not be optimal. The "usual care" comparator must be fully described. There may be differences across jurisdictions in the preferred comparator due to differences in patterns of care.

Additional guidance in comparator selection from ETR experience include:

- Comparators should include those of most interest to Payers and especially existing alternatives already being reimbursed.
- Comparators should reflect established current practise.
- Where there is no reliable gold standard, the use of a sham-controlled study should be considered.
- Consider a pragmatic trial design for the comparator arm when an acceptable 'gold standard' could not be clearly identified, where there are inconsistencies in usual practice across jurisdictions and the technology is not suitable for a sham-controlled study.

Are the health outcomes the important health outcomes?

Health outcomes are outcomes patients experience and care about. Broadly, these include length of life, quality of life, and ability to function. In defining important health outcomes, consideration should be given to patient preferences and trade-offs between benefits and harms. While considered an important additional perspective to policy development, patient preference studies offer a lower quality of evidence and may be inappropriately used to pressurize adoption of a technology. Care needs to be taken to respect the hierarchy of evidence and in particular not to detract from evidentiary methodological considerations outlined throughout this document. Other processes that elicit patient perspectives include focus groups, the Delphi method, the use of citizen councils, crowd sourcing and polling.

Outcome measures should be validated and vetted with a rationale for why the chosen measures are preferred. Minimum important clinical difference should be pre-specified and supported by empirical evidence or expert consensus.

If a surrogate measure is used, its validity and utility as a surrogate must have robust support from an empirical body of evidence.

Harmful outcomes are as important as beneficial outcomes. Rigorous methods of eliciting and reporting harms should be used.

Robust measures of health outcomes are a pre-requisite for analysis of economic value. However, analysis of economic value also requires additional measures such as resource utilization and cost.

Additional guidance on outcomes selection based on ETR experience include:

- Outcomes should be focused on improved direct patient-related outcomes and/or health systems efficiencies.
- Outcomes should only be selected if they are feasible to prove.
- Effectiveness of an existing gold standard against which the technology is being reviewed should be validated.
- Accuracy measures of sensitivity, specificity and likelihood ratios should be used to assess the performance of predictive and prognostic assays.

For medical tests, when direct evidence of improved health outcome(s) is not feasible, is there an empirically-based chain of evidence?

For medical tests, it may not be feasible to conduct an intervention study to assess whether use of the test for direct management improves health outcomes.

Indirect evidence of improved health outcomes requires robust evidence of clinical validity, with complete reporting of performance (true positive, false positive, true negative, false negative).

An empirically-based chain of evidence for the condition and treatment outcomes is necessary to derive benefits and harms from probabilities of true and false results.

Timing – is the duration of follow-up sufficient to observe the important outcomes?

The duration of follow up includes both the trial itself and provisions for longer-term post-trial observation.

2.2 Quality and credibility domains

The Scientific Collaboration has overall responsibility for protocol methodology and thus provides leadership on quality and credibility domains. In reviewing protocols, the Payers' Advisory Committee emphasizes the quality and credibility domains. While a comprehensive approach to examining these domains may be found by examining the GRADE evidence document[6], the following evidence criteria are emphasized:

Control for selection bias, using randomization or an adequate alternative.

Control for perceptual bias, preferably using double-blind design. Or, where double-blinding is not feasible, using an independent assessment of outcomes.

The statistical design and analysis should include adequate power, appropriate statistical tests, and a plan for handling loss of participants or missing data.

Analysis and reporting must permit comparisons to appropriate comparator(s), noting that these might differ across jurisdictions.

Additional quality and credibility through clinical trial design, based on ETR experience

- While examining data from FDA-directed research is important, the evidentiary basis for examining performance and outcomes should reflect evidence-based requirements by PAC.
- The clinical trial construct should provide the most effective and efficient way of satisfying evidentiary requirements for Payers and health professionals. While this is most likely to be through a prospective RCT, other examples are the use of prospective-retrospective study design for examining effectiveness of biomarkers and real time evaluations through evidence with coverage development.
- Advice whether existing evidence is likely to be sufficient to satisfy coverage determination
- Advice whether a planned clinical trial selects outcomes, target populations and comparators relevant to Payers' expectations and whether the quality of the trial is likely to be acceptable.
- Advice whether broadening of the scope of an intended trial to include health professional and Payer expectations is desirable.
- Advice which strategy to use when considering a technology that could be applied across multiple clinical settings, including risk-associated eligibility criteria across multiple settings and sequential trials for each setting.

3. High Level Advice Regarding Implementation Issues

This topic is intended to alert clinical trials methodologists to implementation issues, some of which should be considered for incorporation into protocol development. Some examples of implementation issues appear below:

- Analysis of existing databases to gain a better appreciation of patient outcomes related to comparative technologies.
- Prospective analyses of resource utilization associated with the technology and its alternatives.
- Training requirements for health professionals in the use of the technology.

4. High Level Advice on Coverage and Reimbursement Based on ETRs

- Information on how recommendations by credible professional bodies may inform coverage determination.
- Information on similarities and differences between CMS and private insurers in coverage determination.
- While health economic modeling to test cost-effective thresholds is essential for European, United Kingdom and Canadian health systems and other countries not part of the current EXCITE scope, this is not expected by most U.S. Payers in the evaluation of medical devices. However, U.S. Payers may be influenced if costs are less than a comparator with similar outcomes in the absence of demonstrated superiority. Some Insurers have internal resources applied to cost determinations and budget impact analysis which may not consider company-derived analysis.
- Understanding and application of AMA Current Procedural Terminology (CPT) codes and how these might influence coverage determinations.
- Information on the non-specific code 99 and an explanation of a price threshold for reviewing this code with increasing likelihood of undergoing scrutiny and repeated review for approval with increasing cost of the technology.
- Information on hospital Diagnosis Related Groups (DRG), how this is implemented and funding implications for the company with and without New Technology Add-On Payments (NTAP) for expensive technologies.
- Information on rental costs to test response to allow some Payers to determine long-term coverage, at which time the device could be purchased or continue to be rented if there has been an improvement.
- Importance for Payers to know about compliance if the intent is to purchase the device as an insured benefit. This makes it important to evaluate compliance as part of a clinical trial where this applies.
- Examples of Medicare advice included:
  - Information on broad categories Medicare can pay for, further defined by regulations. Companies need to define these into one of the defined benefit categories to assess whether the technology meets the criteria including being reasonable and necessary and improving patient outcomes. Establishing whether a product fits into a benefit category is a threshold question; if there is no category, an alternative to fee for service would need to be sought.
  - Explanation of applied statutory considerations.
  - Advice on seeking one or more Local Coverage Determinations (LCD) versus a National Coverage Determination by CMS[7].

[7] https://aasm.org/cms-policy-what-are-national-and-local-determinations/#:~:text=CMS%20has%20developed%20two%20types%20of%20coverage%20to,diagnosis%20and%20treatment%20of%20an%20illness%20or%20injury.