Centralized Review of Investigational Device Exemptions at CMS—An IDEa Whose Time Has Come?

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Background: FDA's Changing IDE Policy

An Investigation Device Exemption (IDE) permits a device that has not yet received market approval to be used in a clinical study designed to generate data on the safety and/or effectiveness of such a device. FDA categorizes devices into two categories: Category A or Category B.

- **Category A devices:** "Experimental" investigational devices where the "absolute risk" of the device type has not been established. This category typically includes only FDA Class III devices.
- **Category B devices:** "Non-experimental" investigational devices where the "incremental risk" is the primary risk in question. Class I, II or III can be classified as Category B devices.[1]

IDE trials are often conducted to generate data to support a pre-market approval (PMA) or 510(k) clearance and must receive Institutional Review Board (IRB) approval. When an IDE is submitted for review, FDA can issue one of four decisions: approval, conditional approval, staged approval, or disapproval. Conditional approval or staged approval of an IDE depends on a manufacturer's subsequent response to FDA questions that were not addressed in the initial application, or an FDA requirement that specific conditions be met before proceeding with the study.

The passage of the FDA Safety and Innovation Act of 2012 (FDASIA) changed the Agency's authority for disapproval of an IDE, specifically stating that the FDA "shall not disapprove an IDE" even if: 1) the study may not support a substantial equivalence or approval decision; 2) the investigation may not meet a requirement, including a data requirement relating to the approval or clearance of the device; or 3) the sponsor may need to conduct an additional or different investigation to support clearance or approval of the device.[2]

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[1] FDA Class I, II, or III devices are classified on the basis of risk. A Class I device is considered low enough risk and may even be exempt from a formal notification or PMA application. On the other hand, a Class III device is of the highest risk and will require a PMA with substantial pre- and post-market considerations. Source: FDA, Guidance on IDE Policies and Procedures (January 1998), available at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm080202.htm (accessed Nov. 11, 2013).

[2] FDA, FDA Safety and Innovation Act of 2012 (July 2012), available at: http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf (accessed Oct. 27, 2013).

Predicting the Downstream Impact of FDA's New Policy on IDEs

Since 1995, CMS has allowed for Medicare reimbursement of devices evaluated in Category B IDE trials.[3] Under this regulation, CMS permits local Medicare Administrative Contractors (MACs) to consider coverage for Category B devices that are provided in accordance with an FDA-approved trial protocol within their jurisdiction. CMS also will pay for the costs of routine items and services in Category A and B IDE studies if certain criteria are met.[4] CMS' objective of this policy was to "provide Medicare beneficiaries with earlier access to the latest advances in medical technology while facilitating the collection of information about these Category B IDE devices through clinical trials."[5]

In light of the changes to FDA's IDE policy, we predicted in our previous paper[6] that Medicare would revisit its Category B IDE policy given that the FDA no longer has the authority to disapprove IDEs that previously would have been insufficient to support a device's PMA. In essence, since IDE trial reimbursement was handled at the local contractor level, FDA's previous approach to IDE approvals created a centralized authority to ensure that the planned research would adequately assess device performance.

CMS Proposes to Centralize Review of Category A & B IDE Trials

In the Calendar Year (CY) 2014 Medicare Physician Fee Schedule (MPFS) proposed rule released on July 9, 2013, CMS proposes to centralize the review of Category B IDE trials for reimbursement, rather than continuing to leave such reviews at the discretion of local MACs.[7] In justifying the modification, CMS explains that it had received feedback from the life sciences industry and health care providers that the current local coverage process was "burdensome and created national variability that made it difficult for study sponsors to conduct national IDE studies."[8] The proposed centralized review process

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[3] 42 CFR §§405.20 – 405.215 and §411.15

[4] CMS, Medicare Benefit Policy Manual, Ch. 14, available at: http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c14.pdf (accessed Nov. 3, 2013).

[5] CMS, Decision Memo for Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting (CAG-00085N) (March 2001), available at: http://go.cms.gov/HDC7Jd (accessed Nov. 3, 2013).

[6] Avalere, Implications of the FDASIA 2012 Investigational Device Exemption Provisions (March 2013), available at: http://avalerehealth.net/expertise/life-sciences/insights/fda-and-cms-ask-for-more-collaboration (accessed Oct. 27, 2013).

[7] CMS, CY 2014 Medicare Physician Fee Schedule Proposed Rule (2013), available at: http://www.gpo.gov/fdsys/pkg/FR-2013-07-19/pdf/2013-16547.pdf (accessed Oct. 27, 2013).

[8] Ibid, p. 43343

would require study sponsors to seek Medicare coverage in an IDE trial by submitting their request to CMS' Coverage and Analysis Group (CAG)—the same entity responsible for issuing national coverage determinations (NCDs); studies would receive a single coverage decision accepted by all MACs.

CMS proposes 13 standards that Category A and B IDE studies must meet for the costs of routine care items and services to be eligible for coverage under the centralized process. *See next page for the 13 standards*.[9] These requirements are generally consistent with the clinical trial standards listed in Medicare's Clinical Trial Policy.[10] Further, if the Category A or B IDE trial meets these 13 standards and is a pivotal study with a superiority design against an active comparator, CMS will automatically cover the costs of routine care items and services in the trial. CMS selected these criteria because they believe "the study results will be informative for beneficiary choices and medical decision-making in the real-world settings where most care is actually furnished."[11] It is important to note that while this does not preclude coverage for IDE studies with a non-inferiority trial design, it does offer a fast-track approval process for those that seek to demonstrate superiority to an active comparator and do so in a pivotal study.

[9] Ibid, p. 43343

[10] CMS, Medicare Clinical Trial Policies, available at: http://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/index.html?redirect=/clinicaltrialpolicies/ (accessed Oct. 27, 2013).

[11] CMS, CY 2014 Medicare Physician Fee Schedule Proposed Rule (2013), available at: http://www.gpo.gov/fdsys/pkg/FR-2013-07-19/pdf/2013-16547.pdf (accessed Oct. 27, 2013).

13 Standards Category A or B IDE Studies Must Meet for the Costs of Routine Care Items and Services and the Costs of Category B IDE Devices to be Eligible for Medicare Coverage:

1. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of patients who are represented by the Medicare-enrolled subjects.
2. The rationale for the study is well supported by available scientific and medical information, or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
3. The study results are not anticipated to unjustifiably duplicate existing knowledge.
4. The study design is methodologically appropriate and the anticipated number of enrolled subjects is appropriate to answer the research question(s) being asked in the study.
5. The study is sponsored by an organization or individual capable of completing it successfully.
6. The study is in compliance with all applicable federal regulations concerning the protection of human subjects found at 45 C.F.R. Part 46.
7. All aspects of the study are conducted according to appropriate standards of scientific integrity set by the International Committee of Medical Journal Editors (ICMJE).
8. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
9. Where appropriate, the clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives may be exempt from this standard only if the disease or condition being studied is life threatening as defined in 21 C.F.R. § 312.81(a) and the patient has no other viable treatment options.

10. The study is registered on the ClinicalTrials.gov website and/or the Registry of Patient Registries by the principal sponsor/investigator prior to the enrollment of the first study subject.

11. The study protocol specifies the method and timing of public release of results on all pre-specified outcomes, including release of negative outcomes. The release should be hastened if the study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of ICMJE. However, a full report of the outcomes must be made public no later than 3 years after the end of data collection.

12. The study protocol explicitly discusses subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations in the study. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

13. The study protocol explicitly discusses how the results are or are not expected to be generalizable to subsections of the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

While the proposed process may provide an efficient means for sponsors to secure Medicare coverage for their IDEs, life sciences companies, providers, and other stakeholders have requested answers to the following questions before CMS proceeds with implementation:

- Will CMS' Coverage and Analysis Group (CAG) review the IDE trials and issue the reimbursement decisions itself or will it outsource the responsibility to a single local Medicare contractor?
- If CAG runs the new process, does it have the resources to review the volume of studies that was once managed across multiple local MACs?
- How long will it take for the review entity to issue a coverage decision?
- Will there be an appeals or reconsideration process?
- What will be the composition and the expertise of the review panel?
- What level of interaction should trial sponsors expect with trial reviewers during the process?
- Will existing Category A and B IDE trials still be able to pursue local contractor coverage or does this rule effectively prohibit local contractor review of all IDE trials?
- How will conditionally approved FDA IDE trials be dealt with under this process?
- What level of information will CMS publicly disclose about the trial when it makes its coverage decision?
- Will centralizing the IDE review process serve as a means of horizon scanning for CAG and result in more NCDs?
- If a device IDE is positively reviewed by CMS, does it give that device an advantage if it is subject to an NCD?

Many stakeholders also have raised concerns regarding the definition of a "superiority" trial design necessary for automatic coverage. CMS requires that the comparator group be an "active control." However, there are diseases where no active control therapy has been shown to be safe and effective and so a placebo control is both ethical and scientifically sound.

Policy Implications of a Centralized Review Approach

As emphasized by commenters to the proposed rule, a centralized review approach raises several issues including the serious risks of delay in conducting clinical trial for medical devices as CMS national has finite resources and will have to review a wide variety of device trials. If CAG is the one responsible for reviewing the trials, it will continue to review NCDs with no new appropriated funds coming in to increase their finite resource. FDA receives user fees to review IDEs, whereas CMS does not have access to user fees to centrally review these IDE trials.

Centralizing the review raises an additional issue that traditionally IDE trials were reviewed and approved by FDA before a potentially light touch review by some MACs who then reimbursed for much of the cost of the trial. If CMS begins to review this centrally, it is not clear what the threshold of evidence will be for reimbursement of the IDE trial.

Further, a centralized review approach will likely have differing impacts for small and large manufacturers. For instance, it may benefit small manufacturers as they will not have to use potentially limited resources to contact, engage and convince the many local MACs to cover the costs of their IDE trials. However, the stakes of going through a centralized review process are higher given the all-or-none result. A negative coverage decision from the central entity is binding on all MACs. Currently, a negative coverage decision from a local contractor only eliminates coverage for a single jurisdiction. The manufacturer can still approach other local MACs to obtain coverage. Additionally, under the existing process, manufacturers can elect to target local MACs that are most likely to cover the trial costs based on their reputation for less rigorous review standards and/or the availability of influential local champions for the promising therapy.

Evolving Changes on IDE-Related Policies at the FDA

While the FDASIA 2012 law took away the ability of the Agency to disapprove IDE study designs that may not lead to a PMA, industry has emphasized the importance of feedback from FDA as a leading indicator of whether a device would be found safe and effective in a subsequent pre-market application. In response, earlier this summer, FDA released draft guidance that introduces a new pre-decisional IDE review process. Using this process study sponsors can seek the FDA's input on proposed study designs before submitting an IDE application to the Agency.[12] With this draft guidance, FDA also introduced the concept of "Staged Approval" and "Staged Approval with Conditions," both of which are novel subsets of the previously available "Approval" and "Approval with Conditions" regulatory decisions. Under the staged approaches, FDA either approves or approves with conditions the IDE application, and a subset of the study cohort is enrolled in the clinical investigation while outstanding issues are addressed simultaneously in ongoing discussions between the sponsor and the Agency.

Subsequent to releasing this draft guidance, on October 1, 2013, FDA finalized an additional guidance that specifically created three categories of IDE studies—namely "Early Feasibility Studies," "Feasibility Studies" and "Pivotal Studies."[13] Early feasibility studies

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[12] FDA, Draft Guidance for Industry, Clinical Investigators, Institutional Review Boards, and FDA Staff: FDA Decisions for IDE Clinical Investigations (June 2013), available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf?source=govdelivery (accessed Oct. 27, 2013).

[13] FDA, IDEs for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies: Final Guidance for Industry and FDA Staff (Oct. 2013), available at: http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf (accessed Oct. 27, 2013).

allow a device manufacturer to make minor modifications without prior approval from the FDA and instead have only to submit a report to the FDA within 5 days of making the changes. This differs from traditional feasibility studies which require a 30-day prior notification to, and approval from, the FDA for any changes to a clinical protocol. Further, the approval of early feasibility studies for IDEs may be granted with "less non-clinical data." These are particularly applicable to innovative devices serving unmet medical needs and where there are not alternative safe and effective therapies. In summary, this new finalized guidance creates a new path for early feasibility studies in addition to the previously existing traditional feasibility and pivotal IDE processes.

A Collaborative Paradigm Shift?

It is not clear if CMS' proposed new centralized review of IDEs will allow for coverage of these early feasibility IDE trials discussed with FDA or if new criteria will be developed collaboratively by FDA and CMS in reviewing these types of applications. Many IDE trial designs are for highly experimental breakthrough therapies and they may not have the safety and effectiveness parameters of a traditional feasibility or pivotal study to secure Medicare coverage.

This recurrent theme of the two Agencies—finding synergy while remaining within each of their statutory roles—is further demonstrated by the White House initiated Innovation Pathway program called Entrepreneur-in-Residence (EIR).[14] This is run by FDA and the program created teams that comprised members from CMS CAG in addition to members from Industry, academia and the investor community. One of the initiatives of the EIR program focused on streamlining FDA to CMS approvals for medical devices.[15] This collaborative project has encouraged an increased awareness and opportunity for the two Agencies to look for synergies as they recognize that ultimate patient access to medical devices is not dependent solely on seeking approval from one or other of the Agencies, but requires both.[16] Additionally, as part of the EIR program, the team sought input from private payers, hospital administrators and others in the healthcare supply chain.

Much still remains to be determined, but FDA and CMS clearly are no longer acting in isolation. Increasingly, policy changes in one Agency are triggering reciprocal and coordinated changes in the other, as these two federal authorities continue to work toward a better paradigm through which to deliver healthcare to beneficiaries.

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[14] FDA, Entrepreneurs in Residence Program, available at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/InnovationPathway/ucm286138.htm (accessed Oct. 27, 2013).

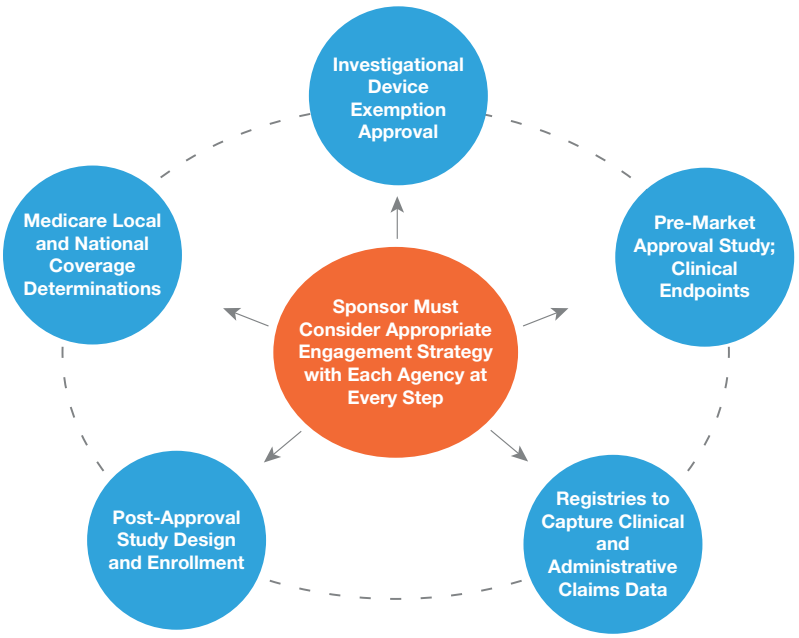
[15] Kern, R. CDRH Entrepreneurs Take Two: Streamlining Data Collection and the Path to Reimbursement. The Gray Sheet (Oct. 22, 2012).

[16] Kern, R. CDRH's Shuren Signals More Guidance, Enhanced Pre-Market Payer Role. The Gray Sheet (Aug. 26, 2013)

For the life science industry, we recommend the following:

- **Evaluate the Final MPFS Rule /** When CMS releases the final rule on or before November 27, 2013, trial sponsors will want to see if and how the Agency has addressed these questions and concerns as their responses will dictate how useful this process is for study sponsors. For example, if CMS keeps its narrow definition of superiority, many device trials will not be eligible for automatic coverage.
- **Efficiencies in Evidence Generation /** As sponsors design clinical protocols for IDE studies, they should take advantage of the fact that CMS will centrally review these studies and design them such that they also may address clinical utility and health outcome measures that may be the subject of coverage-related requirements.
- **Ensure Pivotal Clinical Trials Take Payer Demands into Consideration /** A less burdensome path to get FDA approval of an IDE study or technology does not mean that product sponsors should disregard the evidence requirements demanded of payers, like CMS. Quite the contrary. Particularly with the increased collaboration of the Agencies, it is important for product sponsors to take into consideration the evidence demands of Medicare and other payers before, not after they get FDA approval (see Figure 2).

Figure 2: Leveraging Efficiencies in Evidence Generation



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