Clinical Research: Ongoing Compliance Concerns

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AGENDA

- Post-marketing Research
- Budget Considerations
- Research involving New Software and Technologies
- Investigator Initiated Research
- Proposed Changes to clinicaltrials.gov Reporting
Why Does Industry Conduct Post-Marketing Studies?

- FDA commitment
- Safety
- Expand labeling
  - Additional patient populations
  - New indications
  - New dosages
- Investigator-initiated research

Key Post-Marketing Research Risks

- FDA Regulatory Enforcement
- Anti-Kickback Statute
- False Claims Act

Post Market Research involves unique risks because the products may be subject to reimbursement under federal healthcare programs.
Fraud and Abuse

Anti-Kickback Statute
- Makes it illegal for anyone to knowingly and willfully offer, pay, solicit or receive anything of value in order to induce referrals of, or otherwise generate, Medicare or Medicaid business
- Safe harbor relevant to clinical research services is the Personal Services safe harbor

False Claims Act
- Makes it illegal for any person to knowingly present, or cause to be presented any claim for payment or approval to the federal government that was false or fraudulent
- A manufacturer may be deemed to have caused the submission of a false claim in violation of the FCA if it:
  - Distributes false or misleading information (including off-label information) about its products to prescribers
  - Pays kickbacks resulting in prescriptions of its products for off-label uses

OIG Compliance Guidance

1994 Fraud Alert
Payments which may be deemed improper under the Anti-Kickback Statute include:
- Grants to physicians and clinicians for studies of prescription products when the studies are of questionable scientific value and require little or no actual scientific pursuit
  http://oig.hhs.gov/fraud/docs/alertsandbulletins/121994.html
- Research Funding. . . . Post-marketing research activities should be especially scrutinized to ensure that they are legitimate and not simply a pretext to generate prescriptions of a drug
Affordable Care Act

- Section 6402(f) – “In addition to the penalties provided for in this section or section 1128A, a claim that includes items or services resulting from a violation of this section constitutes a false or fraudulent claim for purposes of subchapter III of chapter 37 of title 31, United States Code”
- Stated another way, in addition to penalties for violating the Anti-Kickback Statute, any claims that were submitted or caused to be submitted, are also subject to the False Claims Act

Suspect Trials

Sham Research
- Features that distinguish sham trials include:
  - Little or no data is being collected
  - Little or no effort required of investigators (aside from prescribing the product)

Seeding Trials
- Some company-sponsored trials of approved drugs appear to serve little or no scientific purpose. Because they are, in fact, thinly veiled attempts to entice doctors to prescribe a new drug being marketed by the company, they are often referred to as “seeding trials”

Seeding Trial Characteristics

- Features of “seeding trials”
  - Study design does not support research goals
  - Selection of investigators based on fact that they are frequent prescribers of competing products
  - Payments to investigators exceed fair market value
  - Studies funded from sales and marketing rather than research department
  - Collection of data that are of little or no value to the company
  - Trials involve introduction of a new drug in a crowded therapeutic class


Questions To Ask

- Who is involved from the manufacturer? Scientific research team? Sales? Marketing?
- Are all the research objectives scientifically valid and driven by research needs? Do they reflect marketing objectives?
  - All clinical research sponsored or funded by the company should be scientifically rigorous and intended to produce valid, useful and non-duplicative data
- Does the research funding exceed fair market value for the research services provided? Confirm services involve substantive research activities.
- Does the arrangement or practice have a potential to interfere with, or skew, clinical decision-making, increase costs to the federal health care programs or increase the risk of overutilization or inappropriate utilization?
- Does the arrangement or practice raise patient safety or quality of care concerns?
Research Budgets and the Anti-Kickback Statute

If a manufacturer provides equipment as part of the study

- Can the institution use it for non-research purposes?
- Can the institution keep it after the study?
- Can Institutions receive discounts on products for which they contributed intellectual property?
- Can they get them for free?

How should embedded manufacturer employees and joint or collaborative research activities be addressed in the budget?

Can researchers be paid for manuscript publication?

How should travel, overhead, fringe benefits and student research tuition be addressed?

Can Investigators get paid directly?
Research involving New Software and Technologies

Software as a Medical Device

- FDA can regulate software, including mobile apps, when it meets the definition of medical device
  - This is an actively evolving area of FDA regulation
  - Exactly which software is subject FDA regulation is not always clear
  - Many software and mobile technology companies are new to the FDA regulated space
- IDE regulations apply to all medical devices, including software
- If the research is IDE exempt, the IRB must review and agree with the manufacturer’s non-significant risk determination
- Failure to do so could cause delays and result in approving a non-compliant study
Example: Does this require an IDE or NSR Determination?

- **Research Purpose:**
  - Evaluate whether the app helps increase healthy lifestyle choices and improve medication adherence and glucose readings.

- **Description of the device:**
  - Mobile App or web-based portal allows patients with diabetes to trend, track and plot glucose readings on graph.
  - Performs simple descriptive calculations – e.g. average glucose readings (day week, month).
  - Not predicting measurements, calculating dosage or changing therapy

- **Description of the device:**
  - App intended to help patients with diabetes maintain healthy, diabetes-friendly diet, track their blood glucose, carb intake, exercise

What about now?

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- **Description of the device:**
  - App intended to help patients with diabetes maintain healthy, diabetes-friendly diet, track their blood glucose, carb intake, exercise
  - Calculate the amount of insulin based on carbs ratio, correction factor, glucose reading and target glucose level, anticipated physical activity and other relevant factors
Other less obvious examples

- Many Institutions and Healthcare Providers are developing software based tools to improve their practice efficiencies and increase patient engagement
  - Care coordination apps automating care protocols
  - Chronic Disease Management tools to take advantage of new telemedicine reimbursement codes
  - Telemedicine portals
  - Remote monitoring platforms to avoid 30 day readmit penalties

- Where is the line between a medical device and practice of medicine?
- Is an Institutions quality committee sufficient?

Institution Review Board – ongoing issues

- **Gelsinger v. Trs. of the Univ. of Pennsylvania** The estate of an 18 yr-old subject of a corrective gene study who subsequently died during the course of the study, filed a complaint naming the trustees of the university and two hospitals affiliated with the research, the investigators, the company that sponsored the research, and the former medical school dean and a bioethicist. *The complaint stated that the IRB of defendant, reviewed and approved the protocol for the OTC gene transfer experiment. The complaint alleged (among other claims) assault and battery linked to a lack of informed consent*. The case settled for an undisclosed amount.

- **Ellen Roche and Johns Hopkins** out of court settlement In 2001, JHU accepted responsibility for the death of a subject. In a report on its investigation into the death, JHU said the researcher who conducted *and the IRB that approved the study had failed to take adequate precautions to protect research subjects*. JHU admitted that the consent form "should not have been approved" by the IRB. *The investigative committee found that the IRB should have required more evidence of safety in the use of the drug*. JHU settled with the family for an undisclosed amount.
Medicare Secondary Payer

- In 2010, CMS issued guidance stating that sponsors of clinical trials are deemed primary payers if the sponsor agrees to pay for injuries to Medicare beneficiaries that arise from the conduct of the research.
- Institutions and Investigators are subject to numerous considerations regarding MSP reporting obligations.
  - Institutions/investigators that are sponsors of human research studies may be required to comply with MSP reporting requirements if they agree to pay for research injuries resulting from clinical trials.
  - Institutions/investigators that conduct clinical research should consider drafting HIPAA Authorizations to clearly state that if payment are made for research related injuries then personal information may be provided to the research sponsor for MSP reporting purposes.
- Penalties: Treble damages for the amount that was improperly paid by Medicare, and CMP of up to $1,000/day for each claim that the sponsor fails to properly report.
MSP Reporting Obligations

- CMS’ MSP Non-Group Health Plan (NGHP) User Guide.
  - An ORM is the sponsor’s responsibility to pay, on an ongoing basis, for the injured Medicare beneficiary’s medical care associated with a claim.
    - CMS guidance states that payment obligations assumed by the sponsor in the CTA for research related injuries should be reported as an ORM.
    - The obligation to report begins when the research related injury arises and continues either quarterly or within 45 calendar days of the assumption of responsibility for payment.
  - TPOC obligations are distinct, and represent the dollar amount of a settlement, judgment, award, or other payment in addition to or apart from an ORM. Sponsor’s obligation to report a TPOC arises only if it settles a claim with a Medicare beneficiary for which it does not have a contractual obligation under the CTA.
    - The reporting threshold is currently $1,000 and must be submitted either quarterly or within 45 calendar days of the assumption of responsibility for payment.

Proposed Changes regarding Clinicaltrials.gov

- Register the trial and submit results information to clinicaltrials.gov.
  - Institutions or Investigators may be a Responsible Party if they are either the sponsor of the study or designated by the sponsor as the responsible party (e.g., investigator-initiated clinical studies).
- Currently, clinical trials results must be submitted for applicable clinical trials of approved, licensed, or cleared products within 1 year of study completion, which may be delayed for up to two years upon certification by the Responsible Party of certain circumstances.
- Expand the current requirement to include applicable clinical trial results of unapproved, unlicensed, or uncleared products.
  - The length of time a sponsor can delay publication of results is the same regardless of whether the clinical trial evaluates the new use of an approved, cleared or licensed product or it evaluates a new product (up to 2 years). HHS decided to impose the same limitation after determining that the benefits of publication outweighed the potential competitive disadvantages this may cause to manufacturers that are developing new products.
More Proposed Changes to Clinicaltrials.gov

- Additional requirements regarding the frequency at which submitted data must be corrected or updated.
  - The proposed rule expands the number of data elements, from two to ten, that must be updated within 30 days of the sponsor becoming aware of the need to update the data.
- PENALTIES: Responsible Parties who fail to comply with registration or results submission requirements may be subject to civil monetary penalties and, for federally funded studies, the withholding of grant funds.

Questions and Resources

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