RESEARCH-RELATED SUBJECT INJURY:
IMPLEMENTING AND OPERATIONALIZING A POLICY THAT WORKS

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Breakout Session 303
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Agenda

- Background
- Legal/Regulatory framework
- Compliance risks
- Benchmarking
- Policy Development and Implementation
- Infrastructure
- Challenges

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BACKGROUND
LEGAL/REGULATORY FRAMEWORK
COMPLIANCE RISKS

Background

- Clinical trial subjects may suffer injury/illness during study participation
- Federal requirements for Informed Consent regarding available care/payment
  - HHS - 45 CFR 46.116(a)(2)&(6) and FDA - 21 CFR 50.25(a)(6).
  - Description of any reasonably foreseeable risks and discomforts
  - For research involving more than minimal risk, an explanation whether compensation and/or medical treatments are available if injury occurs
  - No requirement that payment be offered for subject injury

- Identification of Study Subject Injury (“SSI”)
  - Definitions can be hot issue in negotiations with sponsor
  - Revenue cycle workflows require identification of visits/charges associated with SSI
  - Causation decisions can take time and may be disputed

- Determination of who bears financial burden of diagnosis/treatment of SSI
  - Legally, who can be billed?
  - Ethically
    - Who should bear the financial burden?
    - Participation in a study should not turn on subject’s insurer or ability to pay

- Completion of payment reporting obligations to Medicare
Legal/Regulatory Framework –

Who *Can* Be Billed for Diagnosis/Treatment?

- **Clinical Trial-Specific Contractual Obligations**
  - Variable terms in clinical trial agreements for Sponsor reimbursement of SSI costs
  - Variable promises to subject in ICF to provide medical treatment of SSI at no cost

- **Medicare Clinical Trial Policy – NCD 310.1**
  - Covered routine costs of a qualifying clinical trial include Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service in particular, for the diagnosis or treatment of complications
  - For non-covered items and services, including items and services for which Medicare payment is statutorily prohibited, Medicare only covers the treatment of complications arising from the delivery of the non-covered item or service and unrelated reasonable and necessary care.
  - *All other Medicare rules apply…*
    - Conditions for Payment
    - Medicare Secondary Payor Rule

- **Private Third-Party Payors**
  - Can expressly exclude experimental items/services from coverages
  - Affordable Care Act requires plans cover routine patient costs if appropriately enrolled in an "approved" clinical trial that treats cancer or other life-threatening disease, unless it is a "grandfathered" plan. This may include side effects or problems.
  - State Laws may require coverage of Phase 1-4 cancer clinical trials

Legal/Regulatory Framework –

**Medicare Secondary Payor (“MSP”) Rule**

- **MSP Guidance**
  - §1862(b) of the Social Security Act - [http://www.ssa.gov/OP_Home/ssact/title18/1862.htm](http://www.ssa.gov/OP_Home/ssact/title18/1862.htm)
Legal/Regulatory Framework – Medicare Secondary Payor ("MSP") Rule

MSP Rule
- Beginning in 1980, Congress enacted MSP provisions to shift costs to private payor sources
  - Made Medicare the secondary payor to certain primary plans
  - Prohibits Medicare from making payment where payment is made or could reasonably be expected to be made by a "primary plan"

“Primary Plans”:
1. Certain group health plans, work comp, no-fault insurers
2. Liability Insurance, including self-insurance - insurance that provides payment based on the insured’s alleged legal liability for illness or injury or damage to property.
3. Clinical Trial Sponsors (Study site for self-sponsored studies) are considered to be self-insurers

Legal/Regulatory Framework – MSP Rule - Conditional Payments

Medicare Conditional Payments
- Medicare can make conditional payments if payment has not been made or cannot reasonably be expected to be made promptly by...liability insurance (including self-insurance)...

Definition of ‘promptly’ as to self-insurance payment – MACs follow 42 CFR 411.50:
- Payment within 120 days after the earlier of:
  1. Date a general liability claim is filed with an insurer or a lien is filed against a potential liability settlement
  2. The date the service was furnished, or in the case of inpatient services, the date of discharge

- Primary payors are obligated to reimburse Medicare if they were properly primary to Medicare, but have not paid as primary
- CMS recovers conditional payment if a primary payor is identified
- Provider must return conditional payment within 60 days of identifying primary payor
Legal/Regulatory Framework –
MSP Rule - MSEA§111 Reporting Obligations

MMSEA §111
- Section 111 of the Medicare, Medicaid and SCHIP Extension Act of 2007 ("MMSEA") requires the primary plan report certain information to Medicare about the beneficiary and service provided when the primary plan makes payment to or on behalf of the beneficiary.
  - In 2010, in response to inquiries from pharmaceutical, medical device and biotechnology industry regarding MMSEA Section 111 Mandatory Insurer Reporting language, CMS issued an alert:

  “When payments are made by sponsors (consider site as sponsor) of clinical trials for complications or injuries arising out of the trials, such payments are considered to be payments by liability insurance (including self-insurance) and must be reported.”

WHY REQUIRE REPORTING?
- The reported data allows Medicare to determine who is the primary payor for this and future related services, to track primary payor responsibility and deny future related medical bills, and to seek reimbursement from primary payors who did not pay as primary.
  1. Beneficiary identity – name, gender, DOB, SSN
  2. Incident information
  3. Ongoing Responsibility for Medicals (ORM)

Regulatory Framework –
MMSEA §111 Reporting Obligations

- Identify the Responsible Reporting Entity (RRE) –
  - Industry Sponsor
  - Investigator-sponsor/Site for self-sponsored study
  - RRE can designate 3rd party vendor to manage reporting

- RRE Registration
  - RRE (e.g. Sponsor) must register on the CMS COB Website, and notify Medicare of settlements, judgements, awards or “other payments” made to or on behalf of beneficiaries (e.g. subject injury reimbursements). This allows Medicare to:
    - Determine obligations to pay
    - Track (and deny) future related bills
    - Facilitate recovery of payments/conditional payments

- Ensure process to capture SSI for payment by primary plan

- Identify when SSI payment is to/for Medicare beneficiaries

- REPORT
Legal/Regulatory Framework – Risks

- **Missing Changes in Beneficiary Status**
  - If the injured subject is not a Medicare beneficiary at the time of the injury, the RRE must monitor status and report payments if the subject becomes a beneficiary while providing future related care

- **Penalty for Failure to Report Payment Made**
  - $1000/day penalty for each injured party not reported

Regulatory Framework – CMS Final Rule – MSP Case Appeals for Applicable Plans

- **Final Rule Effective April 28, 2015: 42 CFR Part 45** –
  - Creates right of appeal for MSP determinations relating to liability insurance

Regulatory Framework – Reflection

- ICF promises*
- Identification of relevant services
- Charge Routing
- Release of Information to Sponsors and their 3rd party vendors to meet their reporting requirements – minimum necessary
- Reporting for self-sponsored study injuries
- Ongoing obligations to know beneficiary status while making payments

*To consider for ICF language and billing practice: No-obligation to pay rule
Benchmarking Survey

- Goals of the survey were to gather information about and better understand:
  - How institutions define research-related subject injury
  - Institutional policies for coverage of research-related subject injury
  - How research-related injury is covered for investigator-initiated trials
  - Systems for identifying and managing research-related subject injury
  - Common challenges and solutions

- Methods:
  - SurveyMonkey used to create 16-item survey distributed in June 2014
  - Survey distributed via email to AMCs participating in monthly call organized by the University of California to discuss clinical research billing issues
  - Survey also distributed via networks of cancer centers
  - Survey results discussed during the monthly call organized by the University of California to discuss clinical research billing issues

Survey Questions

- How do you define subject injury?
- For industry-sponsored studies, do you require the sponsor to take full responsibility for subject injury?
- For non-industry sponsored studies, does your institution commit to covering subject injury in the informed consent form?
- Do you have template subject injury ICF language for industry-sponsored studies and non-industry-sponsored studies?
- Do you have a process to identify, report, and track subject injury?
- Who handles requests/invoices to sponsors to cover subject injury?
- Do you have a communication process to adjudicate waivers under your indigency/charity care policy?
- Do you have any insight or lessons learned about defining or managing subject injury that can be shared?
Survey Responses - Summary

- 21 responses received

- General Lessons learned:
  - Most respondents define subject injury as including both known and unexpected risks.
  - A couple institutions specifically qualified their definition with statements excluding risks that would occur in standard of care treatment.
  - Most respondents did not commit to covering subject injury for investigator initiated studies.
  - No clear responses describing a well defined process for identification, management and tracking of subject injury.
  - No clear responses on role of the subject vs. institution in identifying subject injury.

- Specific survey responses...

Please select the best option to describe what is covered as subject injury:

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only unknown risks attributable to study drug/device/procedure</td>
<td>15.7% 3</td>
</tr>
<tr>
<td>All known and unknown risks attributable to study drug/device/procedure</td>
<td>68.42% 13</td>
</tr>
<tr>
<td>Other - Please describe:</td>
<td>16.67% 3</td>
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</table>

Total 19
If the study drug (or other study intervention) is ordinary care but protocol-directed, would related complications or AEs be covered under subject injury?

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
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<tbody>
<tr>
<td>Yes</td>
<td>35.00%</td>
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<tr>
<td>No</td>
<td>59.00%</td>
</tr>
<tr>
<td>Other - Please explain</td>
<td>15.00%</td>
</tr>
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</table>

For industry-sponsored studies, do you require the sponsor to take full responsibility for subject injury as you have defined on the previous page?

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
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<tr>
<td>Yes</td>
<td>70.59%</td>
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<tr>
<td>No</td>
<td>29.41%</td>
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Total 17
For non-industry sponsored studies, does your institution commit to covering subject injury in the informed consent form?

<table>
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<th>Answer Choices</th>
<th>Responses</th>
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<tbody>
<tr>
<td>Yes</td>
<td>26.67%</td>
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<tr>
<td>No</td>
<td>73.33%</td>
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<tr>
<td>Total</td>
<td></td>
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2 of the institutions responding “yes” to this question define subject injury as only including “unknown” or “unanticipated” events.

Definitions of Research-Related Injury

- Injuries or complications arising from the performance of the study in accordance with the protocol or use of the investigational drug or device
- Patient enrolled in a protocol Unexpected Serious Resulting in treatment
- Any injury as a result of subject's participation in the trial, which wouldn't otherwise occur in standard of care treatment.
- Unexpected adverse event directly attributable to the research study
- Complications rising from investigational product
- Injury which can be concluded to be probably or definitely related to a research-related procedure or treatment
Definitions of Research-Related Injury – Cont.

- Injuries or complications (both known and unknown) arising from the performance of the study in accordance with the protocol or use of the investigational drug or device. Study related injuries do not include the normal progression of the subject's disease, injuries or complications that would have incurred had they not participated in the clinical trial.
- Reasonable and necessary medical expenses incurred by research subjects for medical care, including hospitalization, in the diagnosis and treatment of adverse reactions arising directly from or contributed to by research procedures or Study Material following their administration or use in accordance with the Protocol, which are not attributable to the negligence or misconduct of any person in the employment of University. The term "adverse reactions" does not mean the natural progression of an underlying or pre-existing condition or events that would have been expected from the standard treatment using currently approved therapies for the subject's condition.

Sample ICF Template Language

- If you are injured as a result of participation in the research, care will be provided to you. Depending on a number of factors you, your insurance or the sponsor may cover the costs of such treatment.
- *For IITs:* In the event that you are physically injured as a result of participating in this research, emergency care will be available. You will, however, be responsible for the charges for the emergency care. There is no commitment to provide any compensation for research-related injury. You should realize, however, that you have not released this institution from liability for negligence. Please contact the investigator, (name) at (phone number) if you are injured or for further information.
For IITs: The study will not pay for costs associated with treatment of research related injury or illness. We will make every effort to seek reimbursement from your health plan. However, you will be responsible for any deductibles and co-payments required under your health plan and for any claims ultimately denied by your health plan. Financial assistance may be available under institution’s Charity Care Policy and Procedure. If you feel that you have had a research-related injury and need financial assistance, please contact the IRB Office at xxx-xxx-xxxx.
Subject Injury Policy Development

It is recommended that institutions conducting clinical trials establish a Subject Injury Policy that will accomplish the following:

- Include all key stakeholders in policy development
- Define the purpose of the policy
- Clearly define “research-related subject injuries"
- Ensure compliance with CMS research billing rules
- Transparency vs. limiting institutional liability
  - Accurately inform research participants of their financial responsibilities
- Provide direction as to how institution will approach treatment of subject injuries in legal contracts and how those terms will be reconciled with Informed Consent Forms (ICF)
- Develop a policy that can be operationalized by stakeholders

Subject Injury Policy – Key Stakeholders

Institutions will vary – the following is a suggested list of key stakeholders in developing and managing the subject injury process:

- Corporate Compliance Leadership
- Research Leadership
- Finance Leadership
- Risk Management Leadership
- Institutional Review Board
- Sponsored Research Contracting
- Research Billing/Patient Financial Services
- Investigator/Study Team
Subject Injury Policy Development - Purpose

The purpose of the policy should state the scope of the policy's intent.

Example:

“The purpose of this policy is to define, consistent with federal regulations governing informed consent and billing for research-related clinical services, what treatments, coverage for treatments provided, or compensation (if any) will be available to research subjects for a research-related subject injury.”

Defining Research-Related Subject Injury

Basic Elements:

- Cause of injury should be related to research protocol and not standard of care treatment.
- Injury requires diagnosis and treatment
- Balance ethical issues related to protecting subjects from the financial burden of injury while recognizing that industry partners must manage their scope of financial responsibilities.

Example:

“Research-related subject injury” means a medical condition (1) which is caused by and/or directly related to the research study (that is, the condition would not have existed “but for” the subject’s participation in the study), and (2) which is in need of diagnosis and treatment as a matter of medical necessity and standard of care.”
Defining Research-Related Subject Injury

General Exclusions to Consider:

- Attributable to the subject’s underlying medical condition
- Caused by an investigator’s or other physician’s negligence or willful misconduct
- Caused by non-research-related activities.
- Compensation for claims in connection with research-related injuries, such as lost wages, cost of pain and suffering or other additional expenses beyond medical treatment are not covered by this policy.

Policy Development – CMS Compliance

Policies should prohibit scenarios that could result in Medicare becoming a primary payor when another “primary plan” exists.

Example (The Wrong Approach):
Contractual obligation to 1st bill insurance programs for subject injuries, followed by sponsor payment for denied claims.

Result:
- Medicare will be charged for Medicare eligible subjects and Medicare will pay for complications related to Medicare qualified studies.
- Private Insurance Programs will likely deny claims related to research.
- Sponsor becomes the Primary Payor for Private Insurance denials and Medicare is now at a disadvantage.

Impact:
- Medicare Secondary Payor Violation
- Ethical issues related to the indirect cost of billing study subject’s insurance (co-pays, deductibles, insurance caps, etc.)
Policy Development – CMS Compliance

How to avoid Medicare Secondary Payor violations for Subject Injury Claims?

Example (The Right Approach!):
Contractual obligation requires sponsors to pay for all Subject Injuries without an obligation to 1st bill insurance programs, followed by sponsor payment for denied claims.

Result:
- Medicare will not be charged for Medicare eligible subjects and therefore Medicare will remain a “secondary payor.”
- Sponsor is the Primary Payor for all Subject Injuries.

Impact:
- Medicare Secondary Payor compliance.
- Ethical treatment of study subjects by avoiding indirect financial impact from billing their insurance programs for study related injuries.

Policy Development – Transparency vs. Liability

Balancing ethical treatment of study subjects and limiting your institution’s liability for Research-Related Subject Injury (transparency is key).

Positions to Consider:

Industry Sponsored/Initiated Studies – Sponsor pays for all Research-Related Subject Injuries

Investigator Initiated (with treatment interventions – Industry/Fed/Non-Fed) – 1st bill subject’s insurance and if denied, patient will be responsible for denied claims with the caveat that financial assistance may be available under a Medical Center Charity Care Policy.

Investigator Initiated (without treatment interventions – Industry/Fed/Non-Fed) – Subjects informed they will not be responsible for charges associated with care to treat research-related subject injuries.

NCI Cooperative Group Trials – Under CA State law, private insurance programs are mandated to pay for complications arising out of such studies and subjects will be made aware their insurance plans will be charged accordingly. Other state laws will vary.

Transparency Note: For research involving more than minimal risk (as determined by IRB), consent forms must include a description of i) compensation, ii) availability of medical treatment, iii) who to contact in the case of an injury or illness.
Policy Development – Contract Terms & Harmonization with ICF

Clinical Trial Agreements should clearly articulate who will pay in the case of a research-related injury. This is especially true with sponsor-authored/initiated studies. Also critical is consistency between subject injury terms in the CTA and Informed Consent Form (ICF).

Industry Sponsored/Initiated Studies (example):

Sponsor agrees that it will reimburse Institution for the reasonable costs, including hospitalization, it incurs in diagnosing and providing necessary medical treatment to human subjects who are injured as a direct result of the Study Drug or any research procedures performed in accordance with the Protocol, as determined by Institution’s IRB in consultation with the Principal Investigator and Sponsor.

Harmonization between final CTA and ICF:

There must be a process to confirm consistency between the sponsor/institution/study subject financial obligations are consistent with how that information is represented to the subject in the ICF.

Policy Development – Determination & Operations

Who Determines whether an injury is “Research-Related”?

- IRB?
- Principal Investigator?
- Sponsor?

Position to Consider:

- Principal Investigator will assess and report to the IRB whether the injury is research-related.
- IRB will make the final determination in consultation with PI and Sponsor and if determined to be a Research-Related Subject Injury - will coordinate with:
  - Legal Contracting Group (Sponsored Research Office) – Confirm sponsor contractual obligations.
  - Clinical Team – Provide patient information to identify clinical services related to treatment of injury.
  - Research Billing – Provide charges associated with treatment to patient and confirm/correct any charges to insurance programs as appropriate.
  - Risk Management – Assess risk to hospital and prepare notice
INFRASTRUCTURE AND CHALLENGES

Infrastructure

- **Language**
  - Definitions – study subject injury (“SSI”) vs. reportable SAE/UADE
  - Contract - SSI reimbursement terms in research agreements
  - ICF - availability of compensation and/or treatment of SSI, if any

- **Workflows**
  - Revenue Cycle – encounters/charges/claim handling related to SSI

- **Notice**
  - Sponsor
  - IRB – if reportable
  - Risk Management – Hospital/Campus
  - Legal Affairs – Hospital/Campus
  - Professional Liability – Provider/Campus/System
  - Clinical Research Contracts Office
  - Clinical Research Grants Office
  - Clinical Research Billing Office(s) – Hospital, Professional, Compliance

- **Actions**
  - Determination of causation and payor
  - Relationship management
  - Risk management
  - Reporting and Follow-up
Infrastructure

**Tools**
- Bill hold and review of all subject charges during period on-study
- EHR
  - Registration workflows
  - In-basket message upon subject encounter in ED
- CTMS – leverage adverse event entries
  - Potential for interfacing with EHR
  - Automated notices upon entry
- Email, listserv group with interested stakeholders
- Audit Software

Challenges

**Ethical**
- What to cover – is it ethical to hold subjects’ responsible for treatment of research-related injury?
- How to inform subjects
- How to ensure justice/equal treatment

**Financial**
- Financial burden on institution/sponsor
- Institutional liability

**Legal**
- How to ensure compliance with Medicare CTP and MSP rules

**Recruitment/Enrollment**
- Will limiting coverage of research-related injury hinder ability to recruit subjects?
QUESTIONS?