Assumption or Denial of Liability in Clinical Trials: Regulatory, Liability and Reimbursement Issues

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I. Regulatory Considerations

A. Common Rule/FDA Regulations

1. Risks must be minimized and reasonable in relation to anticipated benefits and knowledge to be gained by using sound research design that does not unnecessarily expose subjects to risk and using procedures already performed for diagnostic or treatment purposes where appropriate. (\$111)

2. Informed consent must include (\$116(a)):

For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained[.]

3. And, as applicable, explain (\$116(b)):

Any additional costs to the subject that may result from participation in the research[.]

4. Informed consent must exclude (\$116):

Exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

B. Accreditation Standards (quoted from AAHRPP)

1. The Organization has and follows written policies and procedures for reviewing the scientific or scholarly validity of a proposed research study. Such procedures are coordinated with the ethics review process. (I.1.F.)

2. The Organization has a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate. (I.8.A.)

3. The IRB or EC has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society. (II.3.A)

4. The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (II.3.F.)
C. On the Horizon


Provides a definition of exculpatory language focusing on liability:

OHRP and FDA consider *exculpatory language* to be language which has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault, or guilt. Therefore, a waiver in an informed consent document of any legal right a subject may have may be permissible so long as that waiver does not have the general effect of freeing or appearing to free an individual or an entity from responsibility for malpractice or negligence, or from blame, fault, or guilt (i.e., the waiver is not exculpatory).

Examples of acceptable language:

Because of hospital policy, the hospital is not able to offer financial compensation should you be injured as a result of participating in this research. However, you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital.

Because of hospital policy, the hospital makes no commitment to provide free medical care or payment for any unfavorable outcomes resulting from participation in this research. Medical services will be offered at the usual charge. However, you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the hospital.

In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third-party payer, although you are not precluded from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

Examples of unacceptable language:

I waive any possibility of compensation, including any right to sue, for injuries that I may receive as a result of participation in this research.

If you suffer a research-related injury, neither the institution nor the investigator can assume financial responsibility or liability for the expenses of treatment for such injury.

In the event that you suffer a research-related injury, your medical expenses will be your responsibility or that of your third-party payer.

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2. **Common Rule ANPRM**

   a. No specific recommendations on exculpatory language but proposes to adopt a more risk-based approach.

   b. Little change for more than minimal risk research (with potential exception for IRB oversight process and informed consent documentation).

3. **Presidential Commission for the Study of Bioethical Issues**

   The Commission’s International Research Panel observed that the US is an “outlier in not specifying any system of compensation for research subjects” and recommended development of such a system. The panel did not recommend a particular model though did reference the existing vaccine injury compensation program. Kenneth Feinberg, a victim compensation expert, reportedly testified that these questions should be asked when considering potential models:

   1) Should there be compensation at all?

   2) If you want to compensate, what form will the compensation take? For example, will it include money, medical treatment or loss of future wages?

   3) If it means cash payments, who is paying for it? Is the Government? Is private insurance?

   4) How much compensation?

   5) Who should receive payments? Should it be limited to research subjects or their dependents?

   6) What are the criteria that trigger the payment? Does there need to be negligence, recklessness, or intentional misconduct?

   7) What are the procedures for establishing fact-finding and determination?6

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6 *Id.*
The Commission’s final report to President Obama ultimately concluded that the question requires additional study and the government should explain its reasons for maintaining the (untenable) status quo in the face of multiple prior reports and recommendations.

II. Reimbursement Pitfalls

A. Implications of Reimbursement Policies on Participation and Congressional Response


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7 For a far more in-depth discussion beyond the scope of this presentation, see Janice Ziegler, Holley Thames Lutz, and Rachel Nosowsky, MSP Mandatory Reporting: Implications in the Clinical Trial Context from “Legal and Compliance Issues in Biomedical Innovations Program” (American Health Lawyers Association 2011).

The Conferees have enlarged the scope of the study of third-party payment regarding clinical trials to include cancer and other life-threatening illnesses. The Conferees are concerned that much of the framework for the financing of clinical research is threatened by recent efforts to limit third-party payment for medical and hospital costs. This problem, which has progressed from the exclusion of payment for costs necessitated by the research to the exclusion of payment for any costs if research is conducted, has occurred not just with research on AIDS, but also with research on cancer and other life-threatening illnesses. The Conferees intend that this study review historic, current, and potential practices of private and public payment systems and report back to the Congress on the implications for research and health financing.


B. Medicare Clinical Trials Policy

See Medicare National Coverage Determinations Manual (Pub. 100-3), Ch. 1, § 310.1).

1. Payment for Injuries and Complications

- Treatment of complications arising from participation in a clinical trial, even if the study is not a qualifying clinical trial
- All other rules apply (e.g., treatment must be reasonable and necessary)

2. Exclusions

- Items and services for which there is no benefit category, that are statutorily excluded, or that fall under a national non-coverage policy
- Items and services customarily provided by research sponsors free of charge for any enrollee in the trial

3. Special Note on Medicare Advantage

- Items and services covered under the NCD are paid through the fee-for-service program. This means that providers and suppliers must “split” claims that include both research and non-research items and services, with the research services directed to the MAC and non-research services directed to the MA plan (except in the case of IDE trials covered under 45 C.F.R. part 405, subpart B.
4. **Additional Resources**

- Clinical Trial Policy. Information and resources on the current National Coverage Determination and some but not all historical documents (http://www.cms.gov/clinicaltrialpolicies)

- Medicare Claims Processing Manual, Ch. 32. Billing requirements for special services, including implementation of the NCD (http://www.cms.gov/manuals/downloads/clm104c32.pdf)

- Medicare Provider Reimbursement Manual, Part 1, Ch. 5. Addresses proper treatment of research costs by providers (http://www.cms.gov/manuals/downloads/P151_05.zip)

C. **Medicare Secondary Payer (“MSP”) and the CTP**

1. Since 1980, Medicare has paid for health care items and services furnished to most beneficiaries “secondary” to other insurers, including liability insurers. Primary payers are subject to penalties and providers or suppliers submitting claims to Medicare when a primary payer exists may be subject to exposure under the federal False Claims Act and Civil Monetary Penalties statute.\(^8\)

2. In 2004, CMS issued informal guidance on the Medicare Secondary Payer rule in the form of a letter directed to Holley Thames Lutz. In the letter, the agency articulated its position that a sponsor’s promise to pay research-related injuries is a plan or policy of insurance and, therefore, renders the sponsor a primary payer under the MSP statute – even if the sponsor seeks to limit its exposure by promising payment only in the event the injury is not paid for under the subject’s regular health plan.

3. In 2007, Congress enacted the Medicare, Medicaid & SCHIP Extension Act (“MMSEA”). Section 111 was intended to facilitate more efficient processes for avoiding MSP overpayments by requiring insurers to proactively report on liability payments to Medicare beneficiaries. Failure to report can result in penalties of $1000 per day per violation.\(^9\)

4. In June 2010, CMS posted an “alert” on its MMSEA 111 website. The long-awaited guidance was supposed to clarify MSP reporting obligations of clinical trial sponsors under Section 111 of MMSEA. CMS stated that a sponsor’s promise to pay for injuries or complications sustained in a clinical trial is a form of liability self-insurance which must be reported to a CMS contractor (but did not explain its reasoning).

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\(^8\) See https://www.cms.gov/MedicareSecondPayerandYou/.

\(^9\) See https://www.cms.gov/MandatoryInsRep/01_Overview.asp#TopOfPage.
When payments are made by sponsors 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. The appropriate Responsible Reporting Entity (“RRE”) should report the date that the injury/complication first arose as the Date of Incident (“DOI”). The situation should also be reported as one involving Ongoing Responsibility for Medicals (“ORM”).

Sponsors are faced with the choice of: continuing to cover research-related injuries on a “primary” basis; or not covering any research-related injuries. Some also argue that sponsors may cover only federal health program beneficiaries on a primary basis and all other individuals on a secondary basis.

5. CMS’s legal justification for its position has never been articulated (publicly) in any depth and its policy has never been subject to a rulemaking process. While there is a strong legal basis on which to challenge the position, the policy is relatively clear at this time.

6. Additional Resources:

- Clinical Trials:

- Risk Management Write-Offs:
  [https://www.cms.gov/MandatoryInsRep/Downloads/AlertRiskMgmtWriteOffsNGHP.pdf](https://www.cms.gov/MandatoryInsRep/Downloads/AlertRiskMgmtWriteOffsNGHP.pdf)

- See the NGHP User Guide for the integration and update of these alerts and additional information:

  [http://www.cms.hhs.gov/Manuals/IOM/list.asp](http://www.cms.hhs.gov/Manuals/IOM/list.asp)

- General information on MSP

- Medlearn computer based education and training programs. Includes information on MSP program.
Medicare Coordination of Benefits. Information on the COB contractor

Centers for Medicare and Medicaid Services. Small Employer Exception information

Centers for Medicare and Medicaid Services. Information regarding the mandatory insurer reporting requirements under MMSEA

Medicare Secondary Payer Recovery Contractor. Includes information on CMS MSP recovery efforts.

III. Contracting Considerations

A. Simplification/Standardization Initiatives

1. NCI/CEO Roundtable (2008)

[Subject Injury] Company shall reimburse Research Institution for the direct, reasonable and necessary medical expenses incurred by Research Institution for the treatment of any adverse event experienced by, illness of or bodily injury to a Study subject that is caused by treatment of the Study subject in accordance with the Protocol, except to the extent that such adverse event, illness or personal injury is caused by (a) failure by Research Institution, Principal Investigator or any of their respective personnel to comply with this Agreement, the Protocol, any written instructions of Company concerning the Study, or any applicable law, regulation or guidance, including good clinical practices, issued by any regulatory authority, or (b) negligence or willful misconduct by Research Institution, Principal Investigator or any of their respective personnel. This Section shall survive termination or expiration of this Agreement.

[Indemnification] Company shall indemnify, defend, and hold harmless Research Institution and its trustees, directors and personnel, including Principal Investigator (collectively, the “Indemnitees”) from and against any and all liabilities, damages, losses, claims, and expenses, including court costs and

http://www.cms.hhs.gov/MLNProducts/03_WebBasedTraining.asp

http://www.cms.hhs.gov/COBGeneralInformation/01_Overview.asp

http://www.cms.hhs.gov/EmployerServices/05_smallemployerexception.asp

http://www.cms.hhs.gov/MandatoryInsRep/

http://www.msprc.info/
reasonable attorneys’ fees ("Losses") resulting from or arising out of any third-party claims, actions or proceedings arising out of (i) personal injury to or death of any Study subject enrolled in the Study, which injury or death is caused by treatment of such Study subject in accordance with the Protocol, or (ii) Company’s use or publication of Study Data, in each case solely to the extent that such Losses do not arise out of or in connection with any Research Institution Indemnitee’s (A) failure to comply with this Agreement, the Protocol, any written instructions of Company concerning the Study, or any applicable law, regulation or guidance, including good clinical practices, issued by any regulatory authority or (B) negligence or willful misconduct.

2. Institute of Medicine Public Workshop on Streamlining Clinical Trial and Material Transfer Negotiations (2009)

*Template authored by Jim Snipes, Covington & Burling (SF)*

[Subject Injury] The Sponsor shall reimburse actual and reasonable medical expenses incurred in treating any injury or illness to a Study Subject that is directly related to the administration of the Drug or the proper performance of any other procedure, each in accordance with the Protocol and the Sponsor’s written instructions to the Institution (or to the extent that the Sponsor’s written instructions conflict with the Protocol, the Sponsor’s written instructions to the Institution only). The Sponsor is not required under this Section 3.4 to provide compensation for (a) other injury- or illness-related costs (such as lost wages), (b) medical expenses that are paid for by a third party (provided that neither the Institution nor the Study Subject shall be obligated to seek reimbursement from a third party insurer), (c) medical expenses that are incurred as the result of a violation of the Protocol or other misconduct or negligence, in each case by any agent or employee of the Institution (including the Study Staff), or (d) medical expenses for injury or illness unrelated to the Drug and unrelated to the proper performance of any other procedure required by the Protocol or Sponsor’s written instructions to the Institution.

[Indemnification] The Sponsor shall indemnify, defend, and hold harmless the Institution and its officers, directors, employees, and agents from any loss, liability, damage, or expense (including reasonable attorneys’ fees and costs until such time as the Sponsor assumes the defense) from any claim of bodily injury or property damage that may arise directly from the administration of the Drug or the proper performance of any procedure required by the Protocol or the Sponsor’s written instructions (or if the Sponsor’s written instructions conflict with the Protocol, the Sponsor’s written instructions only); provided, however, that to the extent that the claim is a direct result of (a) the failure of the Institution or one of its officers, employees, or agents (including the Principal Investigator) to follow the Protocol or the Sponsor’s written instructions (each when applicable), accepted medical practice, or Applicable Law, or (b) any other negligence or willful misconduct of the Institution or one of its officers, employees, or agents (including the Principal Investigator), the Sponsor shall have no such obligation, and the Institution shall indemnify, defend, and hold harmless the Sponsor (and its officers, directors, employees, and agents, as applicable) from any loss, liability, damage or expense, but only to 10 the extent arising from any such claim. *[Annotation: A number of public Institutions are barred by statute or state Constitution or internal policy from offering any indemnification.]*
B. Defining Positions

Policies and guidance should be developed at an institutional level to guide negotiations and determine early on whether or not compromise is feasible. Consultation with the IRB regarding what will be acceptable to that body is essential (otherwise a contract might be executable but the study may never be approved).

1. Type of Study
   - Investigator-Initiated
   - Sponsor-Initiated

2. Type of Sponsor
   - Investigator/Institution (Local)
   - Investigator/Institution (Remote – Consortium/Cooperative)
   - Nonprofit/Foundation
   - State/Federal
   - Commercial

3. Type of Risk
   - Subject Injury
     i. Products Liability
     ii. Malpractice/Professional Negligence
     iii. Privacy
   - Breach of obligations to third parties
   - Contractual
     i. Confidentiality of sponsor’s information (direct injury plus regulatory/SEC exposure)
     ii. Regulatory/cGCP violations (resulting in, at worst, exclusion of data and the possibility of market withdrawal)
   - Use of data (by sponsor)
• Fraud and abuse

4. Allocation of Risk

• An internal policy decision first

• For multi-site collaboratives, determine contracting standards via the agreement or, better, though policies approved by executive committee or board

• Unclear policies leave contract negotiators guessing and impede clinical trial negotiations