Clinical Trials: The Shifting Landscape of Informed Consent

September 27, 2018

FDAnews presents EMERGING BIOPHARMACEUTICAL THERAPIES

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Topics for Discussion

Recent changes in informed consent

- Including future uses of biospecimens

Who pays for research-related injury

- Including the Medicare Secondary Payer dilemma

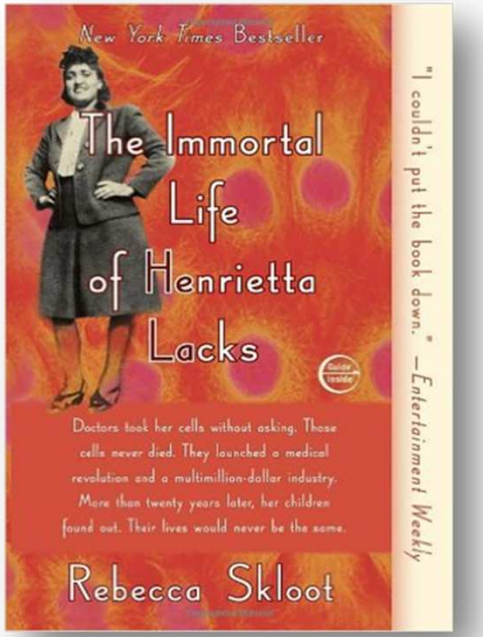
What hospital research contract officers and IRBs are considering

- Including concept of "justice" and research-related injury

Major Changes in Informed Consent – Implications for Research on Biospecimens

Background – Why all the Attention to Biospecimens?

- "Who gets to use my body parts?"
- "Did you make money using a piece of me?"
- "Will scientists pass around my cells without my permission?"



The New York Times

The Opinion Pages | OP-ED CONTRIBUTOR

Your Cells. Their Research. Your Permission?

By REBECCA SKLOOT DEC. 30, 2015

Scientific Advances and Re-Identification

- Ultra-rapid DNA sequencing + big data computation analytics =

  The capability for re-identification of unique previously "de-identified" individuals has been demonstrated

- And, now easy access to public genealogy databases


GENETICS

No Longer De-Identified

Amy L. McGuire[1]* and Richard A. Gibbs[2]

www.sciencemag.org SCIENCE VOL 312 21 APRIL 2006


Identifying Personal Genomes by Surname Inference

Melissa Gymrek,[1,2,3,4] Amy L. McGuire,[5] David Golan,[6] Eran Halperin,[7,8,9] Yaniv Erlich[1]*

www.sciencemag.org SCIENCE VOL 339 18 JANUARY 2013

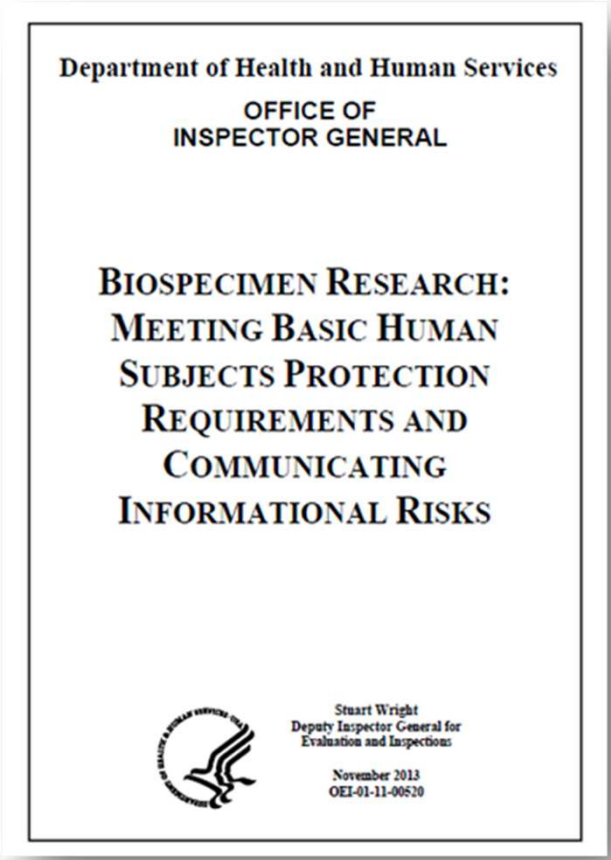

The Washington Post
Democracy Dies in Darkness

True Crime

The ingenious and 'dystopian' DNA technique police used to hunt the 'Golden State Killer' suspect

Informational Risks – OIG is Watching

"…informational risks (i.e., risks related to PII [personally identifiable information]or personal health information), such as a breach of privacy, are magnified because of the long-term electronic storage of the subject's PII and the potential for biospecimens to be used in research not specified at the time of collection."


Department of Health and Human Services

OFFICE OF
INSPECTOR GENERAL

BIOSPECIMEN RESEARCH:
MEETING BASIC HUMAN
SUBJECTS PROTECTION
REQUIREMENTS AND
COMMUNICATING
INFORMATIONAL RISKS

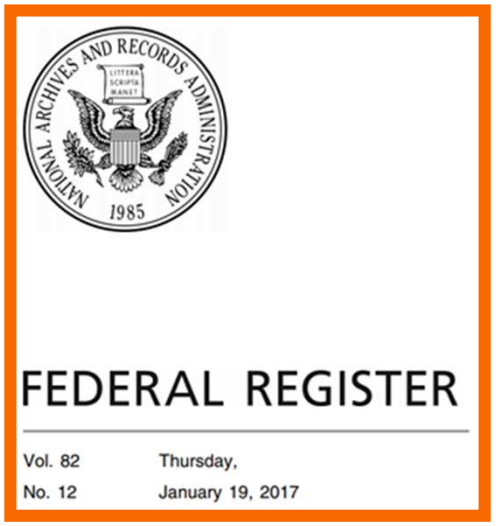
Stuart Wright
Deputy Inspector General for
Evaluation and Inspections

November 2013
OEI-01-11-00520

Game Changer - The Amended Common Rule

— 82 Fed. Reg. 7149 (January 19, 2017)

- Extensively amends the Federal Policy for the Protection of Human Subjects (45 C.F.R. Part 46, subpart A), also known as the HHS Common Rule
  - Revised effective date: January 19, 2019
- 21st Century Cures requires harmonization of FDA regulations not later than December 2019
  - FDA will issue a direct final rule in December 2019



Does Current Common Rule Address Biospecimens?

- No. Neither does 21 C.F.R. Part 50 or 56.

Code of Federal Regulations

TITLE 45
PUBLIC WELFARE

Department of Health and Human Services

PART 46
PROTECTION OF HUMAN SUBJECTS

* * *

Revised January 15, 2009
Effective July 14, 2009

Major Changes Applicable to Biospecimens

- Rule extends the definition of "human subject" to include a living individual about whom an investigator
  - "(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
  - (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens."
- Adds new legal construct of an "identifiable biospecimen"
  - "A biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen."

Major Changes Applicable to Biospecimens

- Rule directly addresses the potential that all biospecimens are potentially identifiable!
  - Requires HHS to conduct (with experts in data matching and re-identification):
    - Reexamination of the meaning of "identifiable biospecimens" and
    - Identification of techniques that generate "identifiable biospecimens"
    - Within 1 year and at least every 4 years

New Basic Element for Informed Consent

For research involving the collection of identifiable biospecimens, a **mandatory statement** that:

- Identifiers might be removed from the identifiable biospecimens and that, after such removal, the "biospecimens could be used for future research studies or distributed to another investigator for future research" without additional informed consent, if this might be a possibility; **or**

- The subject's biospecimens collected as part of the research, even if identifiers are removed, "will not be used or distributed for future research studies."

New Additional Elements of Informed Consent

Disclosures Specific to Potential Future Biospecimen Uses

- **Potential for commercial profit**:
  - "A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit."

- **Potential for genome sequencing**:
  - "For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen.)"

New Alternative for Consent

Broad consent – new!

- An alternative to the requirement for the Basic Elements and Additional Elements. Only applicable for the storage, maintenance, and secondary research use of identifiable biospecimens
- "Secondary research use" is use for either research studies other than the primary research study or nonresearch purposes
- Must include several specific disclosures, including
  - Time periods for maintenance and potential use (may be indefinite)
  - Notification that subject will not be informed of details of research studies that might be conducted and "that they might have chosen not to consent to some of the specific research studies"

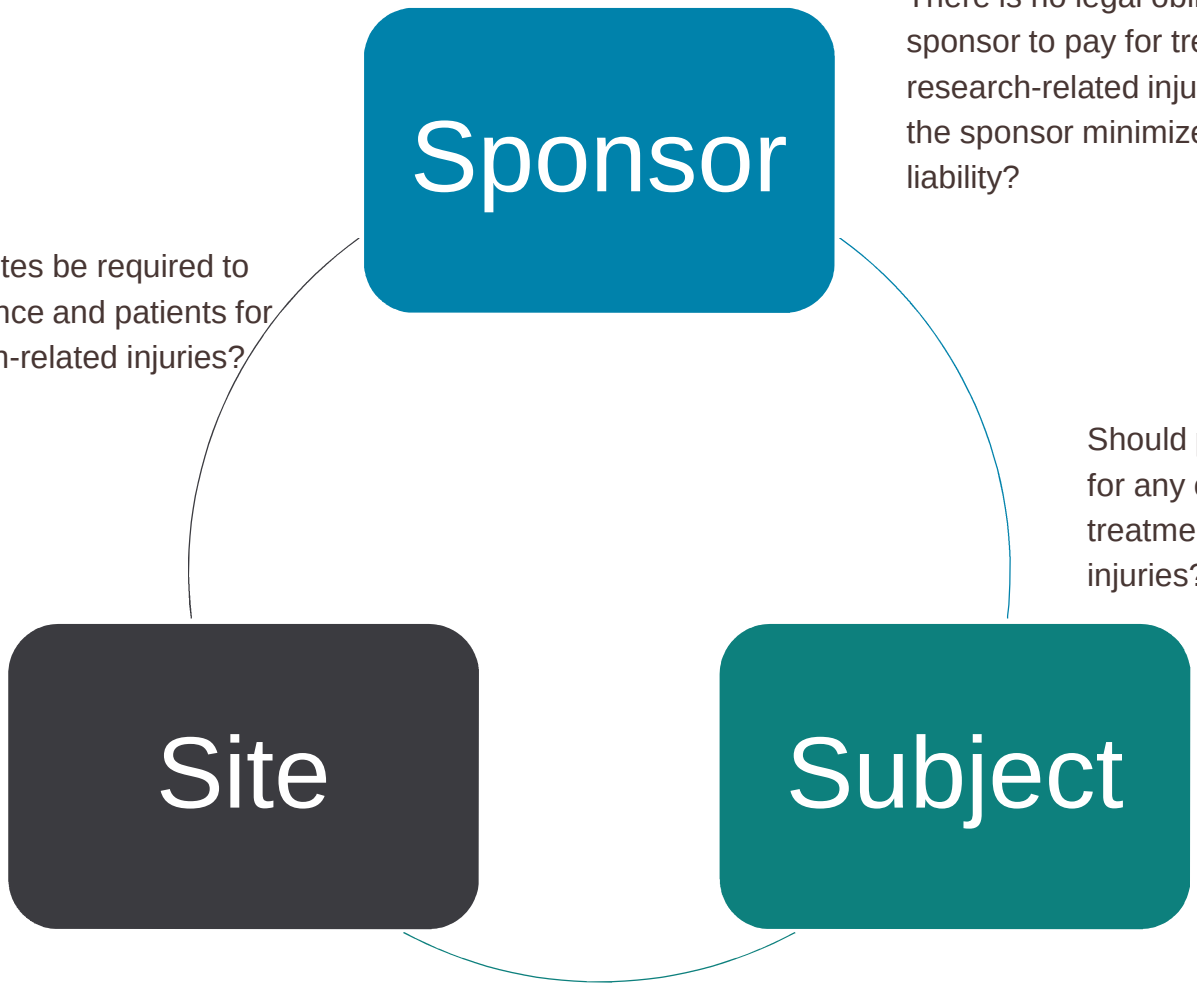
Who Pays for Research-Related Injury?
– The Medicare Secondary Payer Dilemma

Balancing the Interests

There is no legal obligation requiring the sponsor to pay for treatment of research-related injuries—can/should the sponsor minimize its financial liability?

Should clinical trial sites be required to bill third-party insurance and patients for treatment of research-related injuries?

Should patients be responsible for any costs arising out of treatment for research-related injuries?



Broad Medicare Coverage for Research-Related Injuries

National Coverage Determination for Routine Costs in Clinical Trials (310.1)

"Effective for items and services furnished on or after July 9, 2007, Medicare covers the routine costs of qualifying clinical trials, as such costs are defined below, as well as **reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials. All other Medicare rules apply**."

"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**. . . ."

Broad Medicare Coverage for Research-Related Injuries But, the Question CMS Has Not Yet Answered!

National Coverage Determination for Routine Costs in Clinical Trials (310.1)

The NCD explicitly excludes from the definition of "routine costs" that are covered by Medicare any "items and services customarily provided by the research sponsors free-of-charge for any enrollee in the trial"

Does this mean that if a sponsor promises to pay for the costs of items and services for a research-related injury for any single subject that Medicare will not pay for research-related injury costs for any Medicare beneficiaries in the trial?

Medicare Secondary Payer (MSP) Act – SSA § 1862(b)

Prohibits Medicare from making payments for items and services where payment is made or could reasonably be expected to be made by a "primary plan"

"Primary plans" include certain no-fault insurers, group health plans, workman's compensation, and liability insurance, including self-insurance who by contract or other liability are responsible to pay for (or release liability for) medical expense

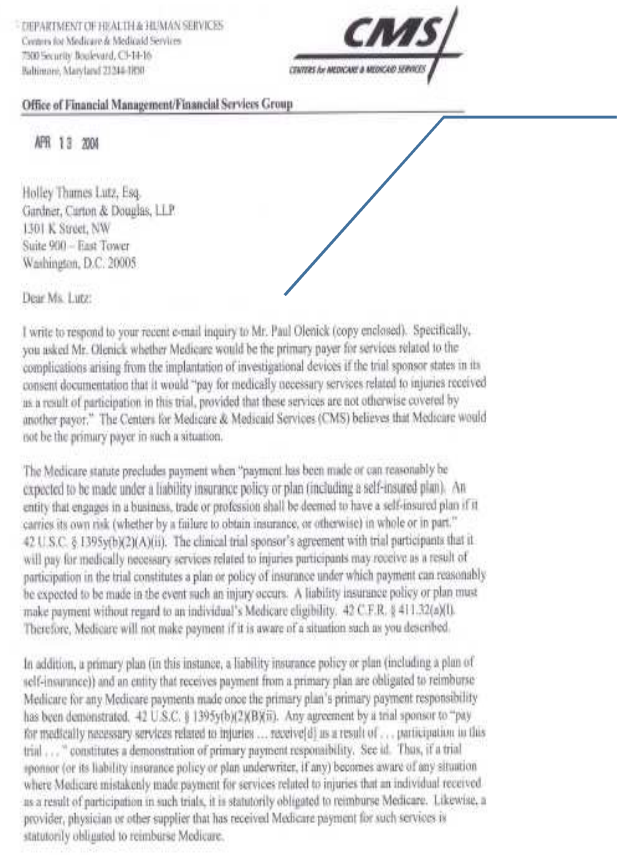
If a "primary plan" has responsibility for the payment, then the primary plan must generally be billed before Medicare

If no primary plan exists at the time of treatment, Medicare may make "conditional" payments, but CMS may later recover from a primary plan or provider that later receives the payment from the primary plan

- Primary plans must reimburse Medicare if they were primary to Medicare but have not paid for the item or service as the primary payer
- Providers must return a payment from Medicare if it identifies a primary payer (within 60 days according to CMS)

Recovery actions can result in double damages, and MSP also authorizes a private right of action for double damages

Are Clinical Trial Sponsors Considered to be "Primary Plans"?



DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Medicare & Medicaid Services
7500 Security Boulevard, C3-14-16
Baltimore, Maryland 21244-1850

CMS
CENTERS for MEDICARE & MEDICAID SERVICES

Office of Financial Management/Financial Services Group

APR 13 2004

Holley Thames Lutz, Esq.
Gardner, Carton & Douglas, LLP
1301 K Street, NW
Suite 900 – East Tower
Washington, D.C. 20005

Dear Ms. Lutz:

I write to respond to your recent e-mail inquiry to Mr. Paul Olenick (copy enclosed). Specifically, you asked Mr. Olenick whether Medicare would be the primary payer for services related to the complications arising from the implantation of investigational devices if the trial sponsor states in its consent documentation that it would "pay for medically necessary services related to injuries received as a result of participation in this trial, provided that these services are not otherwise covered by another payor." The Centers for Medicare & Medicaid Services (CMS) believes that Medicare would not be the primary payer in such a situation.

The Medicare statute precludes payment when "payment has been made or can reasonably be expected to be made under a liability insurance policy or plan (including a self-insured plan). An entity that engages in a business, trade or profession shall be deemed to have a self-insured plan if it carries its own risk (whether by a failure to obtain insurance, or otherwise) in whole or in part." 42 U.S.C. § 1395y(b)(2)(A)(ii). The clinical trial sponsor's agreement with trial participants that it will pay for medically necessary services related to injuries participants may receive as a result of participation in the trial constitutes a plan or policy of insurance under which payment can reasonably be expected to be made in the event such an injury occurs. A liability insurance policy or plan must make payment without regard to an individual's Medicare eligibility. 42 C.F.R. § 411.32(a)(1). Therefore, Medicare will not make payment if it is aware of a situation such as you described.

In addition, a primary plan (in this instance, a liability insurance policy or plan (including a plan of self-insurance)) and an entity that receives payment from a primary plan are obligated to reimburse Medicare for any Medicare payments made once the primary plan's primary payment responsibility has been demonstrated. 42 U.S.C. § 1395y(b)(2)(B)(ii). Any agreement by a trial sponsor to "pay for medically necessary services related to injuries ... receive[d] as a result of . . . participation in this trial . . ." constitutes a demonstration of primary payment responsibility. See id. Thus, if a trial sponsor (or its liability insurance policy or plan underwriter, if any) becomes aware of any situation where Medicare mistakenly made payment for services related to injuries that an individual received as a result of participation in such trials, it is statutorily obligated to reimburse Medicare. Likewise, a provider, physician or other supplier that has received Medicare payment for such services is statutorily obligated to reimburse Medicare.

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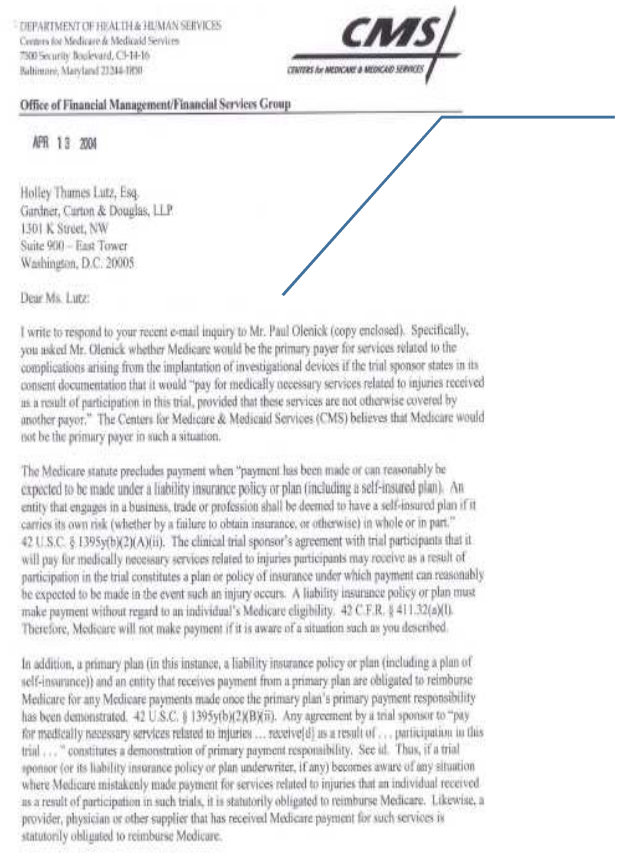
The 2004 CMS Informal Letter continued…



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Letter from CMS Office of Financial Management (April 13, 2004)

In Addition to Repayment, the MSP Act Includes an Obligation to Report Any Payment to, or on behalf of, a Medicare Beneficiary—Including Payment for Research-Related Injury

ALERT:

Clinical Trials & Liability Insurance (Including Self-Insurance), No-Fault Insurance, and Workers' Compensation

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).

May 26, 2010

MMSEA Reporting—The Basics

Section 111 of Medicare, Medicaid and SCHIP Extension Act of 2007 ("MMSEA")

Requires that a "responsible reporting entity" (RRE) register with CMS and report certain information to Medicare when the RRE makes a payment on behalf of or to a Medicare beneficiary

CMS 2010 guidance confirms that RREs include clinical trial sponsors who make payments for research-related injuries suffered by Medicare beneficiaries

How does MMSEA reporting help CMS? It allows CMS a mechanism to:

- Determine who is the primary payer for specific and future services for a specific Medicare beneficiary
- Track a primary payer and identify its responsibility for payments
- Seek reimbursement from a primary payer who did not provide payment for items and services when it should have done so
- Deny payments from Medicare when there is a primary payer

Failure to report could result in penalties of up to $1,000 per day for each instance of non-reporting

Hypothetical

You are a pharmaceutical company and the sponsor of an IND clinical trial of a novel gene therapy product for adults.

You are drafting the Informed Consent Form and must propose a disclosure describing who will pay for the costs to diagnose and treat research-related injury.

- In the next slide, please choose a statement for the Informed Consent Form that tells the subject who will pay for costs to diagnose and treat research-related injury.

- Please select only one answer!

How would you describe who will pay for costs to diagnose and treat research-related injury?

1. Your insurance company will be billed for the costs of any necessary diagnostic tests and treatments for a research-related injury. Depending on your insurance, you may be required to pay a deductible or co-payment or you may be responsible for the full costs if your insurance company refuses coverage.

2. Your insurance company will be billed for the costs of any necessary diagnostic tests and treatments for a research-related injury. If you are a Medicare beneficiary, you may be required to pay a deductible or co-payment or you may be responsible for the full costs if Medicare refuses coverage.
If you have commercial health insurance, the Sponsor will pay for any costs that are not paid by your insurance company.

3. Your insurance company will be billed for the costs of any necessary diagnostic tests and treatments for a research-related injury. The Sponsor will pay for any costs of necessary diagnostic tests and treatments that are not paid by your insurance company.

4. The Sponsor will pay for the costs of any necessary diagnostic tests and treatments for a research-related injury.

Option #1: Sponsor Pays for No RRI Costs

Your insurance company will be billed for the costs of any necessary diagnostic tests and treatments for a research-related injury. Depending on your insurance, you may be required to pay a deductible or co-payment or you may be responsible for the full costs if your insurance company refuses coverage.

- MSP not implicated
- Site and Subject rely on payers for coverage
- Minimal financial exposure for Sponsor
- Issue of coverage for uninsured

Option #2: Sponsor Pays for No RRI Costs for Government Insured Subjects, and Pays for RRI Costs for Others to the Extent Not Paid by Insurance

Your insurance company will be billed for the costs of any necessary diagnostic tests and treatments for a research-related injury. If you are a Medicare beneficiary, you may be required to pay a deductible or co-payment or you may be responsible for the full costs if Medicare refuses coverage. If you have commercial health insurance, the Sponsor will pay for any costs that are not paid by your insurance company.

MSP not implicated

Medicare non-discrimination concerns

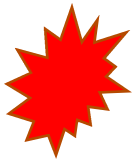
"Free of charge" / "No legal obligation to pay" concerns

Option #3: Sponsor Pays for RRI Costs to the Extent That They Are Not Covered by Third Party Insurance

Your insurance company will be billed for the costs of any necessary diagnostic tests and treatments for a research-related injury. The Sponsor will pay for any costs of necessary diagnostic tests and treatments that are not paid by your insurance company.

"

Traditional "payer of last resort" approach



MSP (reporting <u>and</u> repayment) implicated!

Greatest assurance of coverage for Site and Subject

Issue of Sponsor paying for copays and deductibles for federal health care program beneficiaries

Option #4: Sponsor Pays for All RRI Costs

The Sponsor will pay for the costs of any necessary diagnostic tests and treatments for a research-related injury.

MSP (reporting only) implicated

Greatest assurance of coverage for Site and Subject

Greatest financial exposure for Sponsor

Option #5: Sponsor Pays for All RRI Costs for Government Insured Subjects, and Pays for RRI Costs for Others to the Extent Not Paid by Insurance

If you are a Medicare beneficiary, the Sponsor will pay for the costs of any necessary diagnostic tests and treatments for a research-related injury. If you have commercial health insurance, the Sponsor will pay for any costs that are not paid by your insurance company.

MSP (reporting only) implicated

Good assurance of coverage for Site and Subjects

Financial exposure for Sponsor depends on payer mix

Sponsor Payment of Copays, Coinsurance and Deductibles—The Guidance Is Unclear

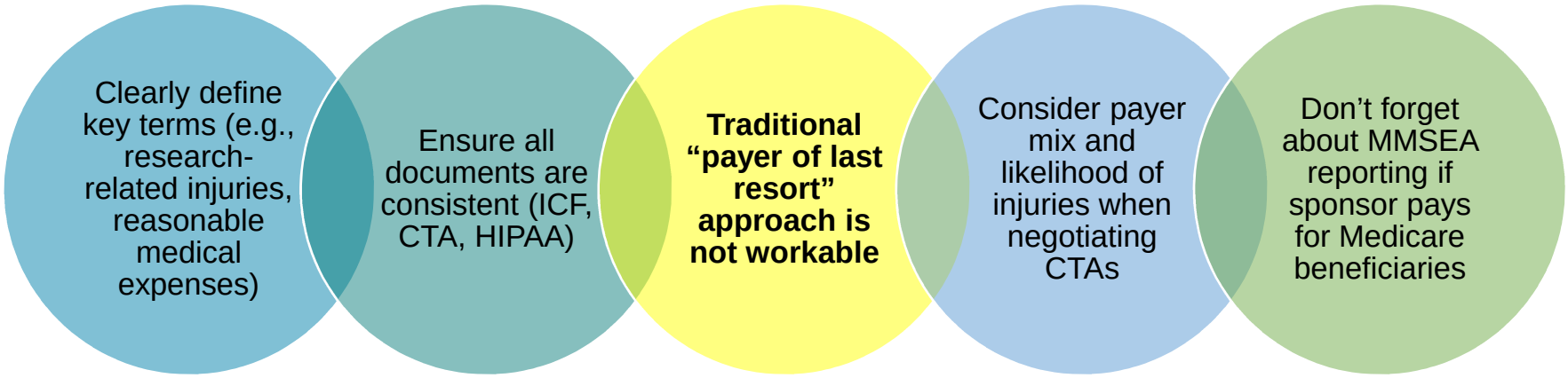
CMS MLN Matters Number SE0822: **Clarification of Medicare Payment for Routine Costs in a Clinical Trial**

Question: May a research sponsor pay Medicare copays for beneficiaries in a clinical trial?

Answer: **If a research sponsor offers to pay cost-sharing amounts owed by the beneficiary, this could be a fraud and abuse problem.** In addition to CMS' policy, the Office of Inspector General (OIG) advises that nothing in OIG rules or regulations under the Federal anti-kickback statute prohibits hospitals from waiving collection of charges to uninsured patients of limited means, so long as the waiver is not linked in any manner to the generation of business payable by a Federal health care program.

The citations include 42 U.S.C. 1320a-7(a)(i)(6); OIG Special Advisory Bulletin on Offering Gifts to Beneficiaries and OIG Special Fraud Alert on Routine Waivers of Copayments and Deductibles.

Key Take-Aways



What Hospital Research Contract Officers and IRBs are Thinking about Informed Consent

General Requirements for Informed Consent

"An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of **coercion or undue influence.**"

"The information that is given to the subject or the representative shall be in **language understandable** to the subject or the representative."

21 C.F.R. § 50.20

Does the disclosure of "who pays" raise an issue of coercion or undue influence?

Are the disclosures complete and understandable in simple language?

Elements of Informed Consent

"(a)(5) A statement describing the extent, if any, to which **confidentiality of records identifying the subject** will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records."

"(a)(6) 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."

"(a)(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to **contact in the event of a research-related injury to the subject**."

"(b)(3) **Any additional costs to the subject that may result from participation in the research**."

21 C.F.R. § 50.25

Will CMS MMSEA reporting requirements breach the sponsor's assertion that the subject's identity will not be disclosed to the sponsor, i.e., that the subject will only be identified by a code with no personal identifiers?

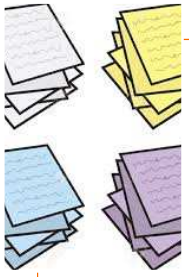
Are all additional potential costs disclosed, including whether subject may be accountable for full payment or co-payment for research-related injury?

How do You Define "Research-related Injury"?

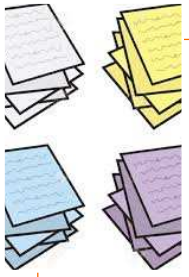
FDA human subject protections describe injury broadly as "research-related injury"

- Not injury limited by a confirmed causal relationship to the test device/drug
- Not injury limited by whether or not the subject and/or investigator fully complied with the protocol

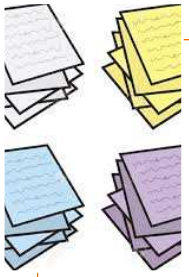
Alignment of Informed Consent Form with Other Legal and Ethical Disclosures



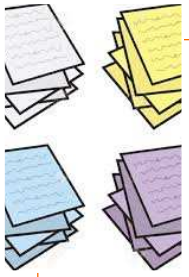
Do the disclosures in the Informed Consent Form about research-related injury align with the CTA between the sponsor and site?



What is the definition that will be used for research-related injury for the specific clinical study?

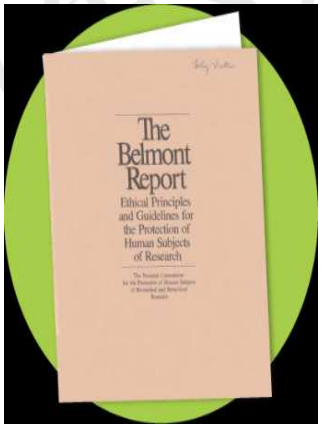


For what period is the disclosure regarding payment for research-related injury applicable? Only during the subject's participation in the trial or later?



Who should review and sign off? on the disclosures? What about the hospital's and sponsor's insurance carriers?

A Growing Concern for the IRB—"Justice"



The Belmont Report

(the foundation for U.S. law and regulations for protection of human subjects)

cites three core principles essential for the conduct of human research

Respect for Persons

Subjects enter research voluntarily and persons with diminished autonomy are protected

Beneficence

"Do not harm" and "maximize possible benefits and minimize possible harms"

Justice

Fairness and equal distribution of the "benefits of research" and "bearing its burdens"

There is an IRB expectation that subjects should not be unequally burdened by the potential for payments for research-related injury—which in certain cases leads to an IRB requirement that the sponsor agree to pay for ALL research-related injury!

Other Concerns of Research Contract Officers

Some considerations specific to
– Gene & cell therapies
– Pediatric research

Thank you

Questions & Discussion!