MSP in the Clinical Trial Context and Other Thorny Issues

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Holley Thames Lutz  
Partner  
T +1 202 408 6836  
holley.lutz@snrdenton.com  
snrdenton.com

F. Lisa Murtha  
Partner  
T +1 202 408 5304  
lisa.murtha@snrdenton.com

Agenda

- General Overview of CTP – Brief Overview
- Medicare Secondary Payor and CTP
- Operational Considerations
- Clinical Trial Billing- Coding
- Medicare Advantage Issues
- Phase I Research and the CTP
Brief Refresher on the Clinical Trial Policy

NCD 310.1 – Clinical Trial Policy

- Provides Medicare coverage for "routine costs" in "qualifying clinical trials", as well as reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials.

- QCT are:
  - Required through the Coverage with Evidence Development (CED) process; or
  - Trials that meet four requirements:
    - Trial evaluates an item or service that falls within a Medicare benefit category, not statutorily excluded from coverage.
    - Trial must not be designed exclusively to test toxicity or disease pathophysiology. It must have therapeutic intent.
    - Enroll patients with diagnosed disease rather than healthy volunteers (therapeutic trials); May enroll healthy patients (Diagnostic trials).
    - The clinical trial must be “deemed” to automatically qualify.
      - 2008 Update proposed self-certification, not implemented
What are Routine Costs in a Clinical Trial?

Routine costs in clinical trials **INCLUDE:**

- Items and services otherwise *generally available to Medicare beneficiaries* (i.e., there exists a benefits category, it is not statutorily excluded, there is not a national non-coverage decision);
- Items and services that are *typically provided absent a clinical trial* (e.g., conventional care);
- Items and services *required solely for the provision of the investigational item or service* (e.g., administration of a non-covered chemotherapeutic agent), the *clinically appropriate monitoring of the effects of the item or service, or the prevention of complications*; and
- Items and 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*.

*Source: Clinical Trial Policy*

What are Routine Costs in a Clinical Trial? (cont.)

Routine costs in clinical trials **EXCLUDE:**

- The *investigational items or services, itself*; unless otherwise covered outside of the clinical trial;
- Items or services *provided solely to satisfy data collection and analysis needs* and that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan); and
- Items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.

*Source: Clinical Trial Policy*
Research Related Injuries under the NCD & MSP Laws

MSP Basics

- The NCD provides coverage for complications:
  - “Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service—i.e., in particular, for the diagnosis or treatment of complications.”
- But, NCD also says all Medicare rules apply. This would include MSP rules.
  - In general, Medicare can not make payment for claims where a “primary plan” has paid or can reasonably be expected to pay for the item or service.
  - “Primary plans” include:
    - Certain Group Health Plans, Workers’ Compensation, No-Fault
    - Liability Insurance (including deemed self-insurance)
      - 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.
MSP Basics

- CMS takes the position that Sponsors are liability insurance plans.
  - Medicare is secondary to any liability insurance plan that is required or responsible to pay based on "legal liability for injury or illness or property damage." (42 C.F.R. § 411.50)

- Primary Payor "legal liability" is established by:
  - A judgment, payment conditioned upon a release (settlement)
  - By other means, including but not limited to a settlement, award, or contractual obligation (42 C.F.R. § 411.22)

- Medicare may make conditional payments, but CMS may recover conditional payments from a primary plan or entity (hospital) that receives payment from the provider plan. 42 C.F.R. § 411.24(h)

- CMS interprets 411.24(h) to require entities (providers) that receive duplicate primary payments to reimburse Medicare within 60 days.
  - Underscored by PPACA § 6402

MSP Basics – Damages

- MSP rules provide for double damages for a primary plan sued by the Government for recovery.

- MSP laws authorize a private right of action with such recovery.
  - U.S. v. Eastern Oklahoma Orthopedic Center. Qui tam action against the Eastern Oklahoma Orthopedic Center for failing to disclose the existence of primary payers on Medicare claims, and retaining overpayments under the MSP laws that should have been refunded to Medicare.
    - Held: Defendant's purposeful omission of information regarding secondary payers resulted in the receipt of unwarranted Medicare payments, in violation of the FCA

- PPACA 60-day overpayment refund obligations add further complexity
Section 111 of the Medicare, Medicaid and SCHIP Extension Act of 2007 ("MMSEA") requires primary plans to report certain data to CMS regarding settlements, judgments, awards or other payments of claims where injury or illness of Medicare beneficiaries is at issue.

- Plan’s failure to report could result in CMPs of $1000 per day for each instance of non-reporting.

- Helps CMS to identify amounts paid to Medicare beneficiaries (or providers under assignment) as a result of claims brought against insurers, self-insurers or insured entities where a portion of the payment covers medical care that has been, or will be, covered by Medicare.

- This is not a substantive expansion of MSP, but rather a requirement to affirmatively submit information to facilitate CMS collection efforts under the MSP laws.

CMS-MSP-RRI-MMSEA...Stop the madness!
How does this all fit together?

- The CTP provides Medicare coverage for “[i]tems or services needed for reasonable and necessary care … for the diagnosis or treatment of complications.”
- CTA/ICDs may include Sponsor’s agreement to pay for reasonable costs of treatment for subjects who are injured solely as a result of enrolling in the trial (i.e., not injuries related to natural disease progression, protocol deviation, etc.), if no other payment is available.
- Does this promise trigger MSP laws such that Sponsor should pay primary to Medicare (or be responsible for refunding conditional payments if Medicare did, in fact, pay first)?
  - CMS says YES, this promise to pay triggers MSP rules and Sponsors, not Medicare, are responsible for payments for RRI.

In Short….

- CMS’ 2004 Informal Position in the “Lutz Letter”:
  - “The clinical trial sponsor’s agreement with 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.”
  - “[CMS] believes that Medicare would not be the primary payor in such a situation.”
- Remember: Medicare is secondary to any liability insurance plan that is required or responsible to pay based on “legal liability for injury or illness or property damage.” (42 C.F.R. § 411.50)
- CMS Rationale:
  - Sponsor promise = liability insurance policy or plan (sponsors may be self-insured)
  - Sponsor’s “agreement to pay for RRI” = de facto “demonstration” of Sponsor’s responsibility to pay
- June 10, 2010, CMS issued a three-sentence alert (dated May 26, 2010) related to MMSEA § 111, that “clarifies” that Sponsors paying for RRI are considered to be payments from liability plans, and must be reported to CMS.
  - http://www.cms.gov/MandatoryInsRep/Downloads/AlertClinicalTrailsNGHP.pdf
Operational Issues

Impact on Providers

- Prior to June 2010, CMS guidance was only informal to one industry counsel ("Lutz Letter"), though note all Regional Offices were cc'd. Many providers took issue with the guidance, as did Sponsors.

- Now that CMS has set forth its CTP guidance, albeit in the MMSEA context, Sponsors are more cognizant of potential damages of $1000/day per non-reported event, and may take this position more seriously, impacting CTA negotiations.

- If Sponsor, provider, physician or other supplier becomes aware of any situation where Medicare mistakenly makes payment for RRI under such an agreement, it is "statutorily obligated to reimburse Medicare."

- Potential for identified overpayments and 60-day refunds.
Options on CTA Language to Avoid MSP Issues

- Eliminate the Sponsor’s promise to pay for RRI and bill Medicare per CTP. (Drawbacks for sites)

- Sponsor promises to pay for costs associated with RRI for FHCP beneficiaries, so no billing to Medicare; but commercials are billed first. (Drawbacks for commercials)

- Sponsors agree to pay for all RRI regardless. (Drawbacks for Sponsors)

Is that the last word?

- While it is important to comport behavior to the regulator’s articulated rules, there remain some potential challenges (or at least questions) to CMS’ position.

- From the MMSEA Reporting front, there must be a “claim” that is resolved through “settlement or judgment … or other payment,” and a claim must be filed by a “claimant,” which could be subject or entity “insured or covered by the … plan.” There are arguments that short of a true claim to the Sponsor and a release, perhaps the application of Section 111 to clinical trials remains suspect.

- From the MSP front, even if CMS claims that it is settled that a Sponsor is a “liability plan” subject to MSP rules, there still must be “liability” of the Sponsor. If a Sponsor offers to pay, not because it’s liable, but out of ethical considerations, are they really “liable” under MSP doctrine?
  - If the Bill and Melinda Gates Foundation agree to pay for all MRIs associated with an oncology study, is there liability? Generally rooted in tort context.
  - 2006 Interim Final MSP Rule added liable through “other means, including contractual obligations. So, a bit difficult, but not impossible to argue in good faith.
Hypothetical Situations

- Each of the following scenarios assumes that: (i) an individual suffered complications or was injured as a direct result of his or her participation in a clinical trial; (ii) institutional policy and the governing informed consent document both permit billing Medicare and third party payers for such complications, consistent with their respective policies and guidelines; (iii) the sponsor (if any) has agreed to pay for the cost of treatment in these circumstances; and (iv) there is no independent promise or commitment from the site/provider to pay future medical costs.

Hypothetical- A

- All items and services necessary to treat the complication or injury are waived or written off (as far as the research participant is concerned).
Hypothetical- B

- Same facts as A, but the study is investigator-initiated and the site writes off 50% of charges rather than the entire claim.

Hypothetical- C

- Items and services necessary to treat the complication or injury are billed to insurance, but subject has threatened to sue, is completely uncommunicative, and accordingly coinsurance is deemed “uncollectible.”
Hypothetical- D

- Items and services necessary to treat the complication or injury are billed to insurance, but subject qualifies for assistance under the medical center's charity care/indigency policy.

Clinical Research Billing- Coding
Clinical Research Billing- Coding

- Medicare requires certain codes and modifiers to be used for claims submitted for routine costs during
- January 18, 2008 Transmittals
  - Q0/Q1 Modifiers (Transmittal 310)
  - Clinical Trial Number Option (Transmittal 1418)

- Status:
  - V70.7 code: required
  - Modifiers: required in outpatient setting
  - Clinical Trial Number: optional

- Note: if there is billing during a non-QCT, then the services would not need the CRB coding because the services would only be billed because they are scheduled for the patient's care and only secondarily may be used for data collection.

V70.7 Code

- V70.7 is a diagnosis code which means “examination of participant in clinical trial”
- The V70.7 is required for all Medicare claims which contain “routine costs”
- The V70.7 is the provider’s attestation that the claim contains routine costs during qualifying clinical trials
- For billing “routine costs,” the V70.7 is listed as the secondary diagnosis
- If the V70.7 is listed as the primary diagnosis, then the claim will be denied
Condition Code 30

- Institutional Inpatient Claims:
  - “Institutional providers billing clinical trial service(s) must report a diagnosis code of V70.7 in the secondary position (or in the primary position if the patient is a healthy, control group volunteer) and a condition code 30 regardless of whether all services are related to the clinical trial or not.”

- Outpatient Claims:
  - “On all outpatient clinical trial claims, providers need to do the following:
    - Report condition code 30,
    - Report a diagnosis code of V70.7 in the secondary position (or in the primary position if the patient is a healthy, control group volunteer)”

- Medicare Claims Processing Manual, Ch. 32, Sec 69.6

CRB Modifiers

- Medicare CRB Modifiers:
  - Q0: “investigational clinical service”
  - Q1: “routine clinical service”
- Applied to claim form per CPT code
Timing of Modifiers

- The research modifiers only apply to the routine costs being billed to Medicare or the rare instances of an investigational clinical service being billed to Medicare.
- The research modifiers' timing is triggered by the patient signing a research informed consent form, but only the study-related services require a research modifier.
- Services that occur after consenting which are not related to the study, do not require a modifier.
- (Also: an encounter that has no relation to the study and contains no “routine costs,” does not require a V70.7)

Q0 Modifier

- “Investigational clinical services are defined as those items and services that are being investigated as an objective within the study. Investigational clinical services may include items or services that are approved, unapproved, or otherwise covered (or not covered) under Medicare.”
**Q1 Modifier**

- “Routine clinical services are defined as those items and services that are covered for Medicare beneficiaries outside of the clinical research study; are used for the direct patient management within the study; and, do not meet the definition of investigational clinical services. Routine clinical services may include items or services required solely for the provision of the investigational clinical services (e.g., administration of a chemotherapeutic agent); clinically appropriate monitoring, whether or not required by the investigational clinical service (e.g., blood tests to measure tumor markers); and items or services required for the prevention, diagnosis, or treatment of research related adverse events (e.g., blood levels of various parameters to measure kidney function).”

**Modifier Examples**

- **Drug Study:**
  - Diagnostic testing: Q1
  - Treating complications: Q1
  - Administering study drug: Q1
  - “Imaging service at Week 8 to determine effectiveness of timing of image”: Q0
Medicare Advantage Issues

What is Medicare Advantage?

- Medicare Advantage is an optional program for seniors that provides the same benefits as Medicare Part A (inpatient insurance) & Part B (outpatient and physician insurance) but may include lower co-insurance, lower or no deductible, and additional benefits for either the same premium as Part B or slightly higher.
- Medicare Advantage is “Part C” of Title XVIII of the Social Security Act.
- Medicare Advantage is formerly known as:
  - Medicare + Choice
  - Medicare Managed Care
Medicare Advantage

- CMS contracts with private insurance companies to administer Medicare Advantage benefits; these are referred to as Medicare Advantage Plans (MAPs)
- The MAPs compete for seniors to enroll in the same way Part D Prescription Drug Plans compete for enrollment
- Medicare Advantage enrollment varies around the country
- 30% to 35% of seniors in the U.S. are enrolled in a MAP

Medicare Advantage & CRB: General Rule

- Clinical research study-related services are covered for Medicare Advantage enrollees, but where the claims are sent follows different rules for non-device studies
  - **Device trials:** Research-related services during device trials are billed to MAP in the same way (Medicare Managed Care Manual, Ch. 8, Sec. 40.4.4)
  - **Non-device trials:** Research-related services are billed to the provider’s “Original Medicare” contractor (i.e., the same contractor where Part A & Part B claims are sent) (Medicare Managed Care Manual, Ch. 8, Sec. 40.4.3)
- **Impact:** Not only must all research patients be flagged in the CRB process, but the billing system must direct all research-related claims for Medicare Advantage patients to the Original Medicare contractor
Basic Rule

- Medicare Claims Processing Manual, Ch. 32, Sec. 69.9:
  - “For dates of service on or after September 19, 2000, and until notified otherwise by CMS, Medicare contractors will pay for covered clinical trial services furnished to beneficiaries enrolled in managed care plans.”
  - “Determine payment for covered clinical trial services furnished to beneficiaries enrolled in managed care plans in accordance with applicable fee for service rules, except that beneficiaries are not responsible for the Part A or Part B deductibles (i.e., assume the Part A or Part B deductible has been met). Managed care enrollees are liable for the coinsurance amounts applicable to services paid under Medicare fee for service rules.”

MA Clinical Trials Rule- No Impact on Device Trials

- Medicare Managed Care Manual, Sh. 8, Sec. 40.4.4:
  - “Medicare Advantage organizations should not confuse clinical trial coverage under the September 2000 NCD with Medicare's policy on IDE (Investigational Device Exemption) coverage. Category B IDE trials have been covered, at contractor discretion (within CMS's rules and guidelines), since November 1, 1995, under 42 CFR 405.201 to 405.215. Category B IDE costs are included in the Medicare Advantage (MA) payment rates. Therefore, these claims are not paid on a fee-for-service basis by fiscal intermediaries and carriers. The MA organizations can apply plan rules, including prior authorization rules, when determining whether to cover an enrollee’s participation in a Category B IDE trial.”
Medicare Advantage & CRB: Patient Implications

- Patient out-of-pocket implications:
  - Deductible is allowed to be waived
  - Sending claim to Original Medicare generates Part B co-insurance (co-pay)
  - Part B co-insurance is **not** allowed to be waived
  - Co-insurance for Part B is 20% of Medicare rate

- Impact:
  - Medicare Advantage patients enrolled in clinical trials generally have higher co-pays for the covered services
  - CMS recognizes this and is contemplating a rule change for 2011 in which the MAP will be required to reimburse the patient for the difference between the MAP co-pay and the Original Medicare co-pay
  - However, 2011 proposed “fix” does not change the provider’s obligation to redirect the claims to the Original Medicare contractor

Medicare Advantage & CRB: Compliance Implications

- Billing a MAP when the Original Medicare contractor should have been billed could create an overpayment situation
- MAPs are contractors for the Medicare Program
- MAPs negotiate a rate with CMS for each senior who enrolls in the MAP
- Billing a MAP when a provider should not involves a MAP paying funds which it should not
- The U.S. False Claims Act was amended in 2009 to include “contractors” of the United States government

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Do patients know about this rule?

- CMS would say they do
- FAQ from Medicare beneficiary information booklet about clinical trials (March 2010):
  - I’m in a Medicare health plan. Can I still be in a clinical research study?
  - Yes. If you’re in a Medicare Advantage Plan (like an HMO or PPO) or other Medicare health plan, you can get the same coverage for clinical research studies as a person in Original Medicare, as described in the previous section. Once you join a Medicare-covered clinical research study, Medicare will pay for your covered services as if you were in Original Medicare. This means that your Medicare health plan can’t keep you from joining a clinical research study. However, you should tell your plan before you start a study. That way, the plan can still keep track of your health care services and explain what you will have to pay for copayments, coinsurance, and deductibles.

Which services are billed to Original Medicare?

- Services that are “related to the clinical trial” are billed to Original Medicare
- Services that are “unrelated to the clinical trial” are billed to the MAP
- CMS does not provide clear guidance as to when something is “related to” or “unrelated to” a clinical trial
  - Organizations should establish a consistent approach that uses good faith interpretations
  - Common approach:
    - “related to” refers services scheduled by the protocol and services to treat complications;
    - “unrelated” refers to unscheduled services that are not the result of being enrolled in the study
Which services are billed to Original Medicare?

- **Practical approach**: Use the MCA as a guide
- **Possible scenarios**:
  - If the service is on the MCA (because it is scheduled by the study), then the service should be billed to Original Medicare
    - Example: protocol scheduled drug infusion
  - If the service has nothing to do with the study and is not scheduled by the protocol, then bill to the MAP
    - Example: patient complaint of back pain requires imaging services
  - If the service is to treat a complication related to the investigational item, then the service should be billed to Original Medicare
    - Clinical research coordinators should inform the CRB process of when treatment of complication occurs

Split-billing on “mixed” days

- If the encounter includes some services which are related to the research study and some which are not related to the research study, then charges for the encounter must be “split”
- Split billing usually refers to directing charges from the same day to different payors
- It is important to split bill for “mixed” research days because if the entire claim is directed to the Original Medicare contractor, then the MAP inappropriately benefits (by not having to pay) and the patient must pay unnecessary co-pays
- **The CRB process must know**:
  - Which encounters include protocol-related services
  - Which charges are related to the research study (the MCA shows this)
Medicare Claims Processing Manual

- Medicare Claims Processing Manual, Ch. 32, Sec. 69.9
  - “[F]or beneficiaries enrolled in a managed care plan, institutional providers must not bill outpatient clinical trial services and non-clinical trial services on the same claims. **If covered outpatient services unrelated to the clinical trial are rendered during the same day/stay, the provider must split-bill so that ONLY the clinical trial services are contained on a single claim and billed as fee-for service**...Any outpatient services unrelated to the clinical trial should be billed to the managed care plan.” (emphasis in original)

Review of Provider Settings

- **Hospital outpatient setting**: Encounters including research-related services must be reviewed for potential split-billing
- **Physician professional fees**: Encounters including research-related services must be reviewed for potential split-billing
- **Inpatient care**: CMS is not clear on the impact for split-billing. An inpatient claim cannot be “split.” The CMS split-billing references are for outpatient services.
  - Options:
    - If the reason the patient is admitted is unrelated to the study, then send claim to MAP
    - Keep “routine cost” charges off the UB claim form for MAP patients or place in non-covered column
    - Pre-authorize with MAP
    - Use v70.7 code
Likely changes in 2011 could increase audits/reviews

- CMS has not released a final rule, but in April 2010 the agency announced that it would likely require MAPs to pay the co-pay differential.
- This will make the patient “whole” and the patient will not have additional out-of-pocket expenses for enrolling in a research study.
- Likely effect: MAPs will be paying more under this new arrangement and the MAPs will likely be watching carefully what services during a clinical trial are being billed to Original Medicare to ensure that the MAP is only paying legitimate co-pay differentials.
- In other words, it would not be surprising to find more CRB reviews being conducted by MAPs.

Phase I Research and the Clinical Trial Policy
Phase I Research and CMS’ Standards and Statements

- CTP “not designed exclusively to test toxicity” vs. “principal purpose”
  - 2006: AHLA Audioconference and Q&As:
    - Question: “Is it sufficient for a trial to ‘observe for therapeutic benefit’ to meet this ["therapeutic intent"] requirement?
    - CMS Response: “The phrase ‘therapeutic intent’ is open to interpretation. The purpose of this requirement is to exclude clinical studies to evaluate the toxicity or adverse events solely.”
  - 2007: CMS proposed revision via reconsideration of 310.1: “The research study is not designed to exclusively test toxicity or disease pathophysiology. Research studies, including some Phase I trials, whose protocols commit to measuring therapeutic outcomes as one of the objectives, may meet this standard only if the disease being studied is chronic, life threatening, or debilitating.”
    - Not adopted…though see PPACA
    - Based on FDA definition

FDA and NIH Definitions Cited as Not Supporting TI

- Absent CMS standard, there are two definitions often cited by contractors as basis for excluding coverage of Phase I studies because there is no “therapeutic intent.”
  - FDA:
    - Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness….
    (www.fda.gov/cder/handbook/phase1.htm)
  - NIHGPS (10/10)
    - Phase I. Tests a new biomedical intervention in a small group of people (e.g. 20-80) for the first time to determine efficacy and evaluate safety (e.g., determine a safe dosage range and identify side effects).
NIH and Other Definitions In Support of TI

- **FDA (use as a sword, not just contractor shield)**
  - Use FDA definition for support as it indicates, “and, if possible, to gain early evidence on effectiveness.”

- **ClinicalTrials.gov**:
  - Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.

- **NIH NCI Investigator’s Handbook**:
  - Phase 1 trials determine a safe dose for Phase 2 trials and define acute effects on normal tissues. In addition, these trials examine the agent’s pharmacology and may reveal evidence of antitumor activity. Therapeutic intent is always present in Phase 1 trials; indeed, anticancer agents are not tested in patients unless preclinical activity studies have already demonstrated evidence of significant activity in laboratory models. ([http://ctep.cancer.gov/investigatorResources/docs/hndbk.pdf](http://ctep.cancer.gov/investigatorResources/docs/hndbk.pdf))

Regional Interpretations

- When a Medicare policy is not clear, the local Medicare Contractor is allowed to interpret the policy
  - Highmark has stated to a University that, “based on the FDA definition of a phase 1 clinical trial, and the guidelines provided by [CMS] in NCD 310.1, Highmark … does not reimburse for routine costs associated with a phase 1 clinical trial as, by definition, phase 1 clinical trials are designed to determine the metabolic and pharmacologic actions of the drug in humans, and not specifically with therapeutic intent.”
  - Palmetto GBA has indicated to one provider, based on the broader NIH definition in the NIHGPS, Phase I do not have therapeutic intent. (Note, this jurisdiction is likely less definitive than Highmark)

- Medicare Contractors slow to take up the cause…not such a bad thing.
Take-Away and Recommendations

- CMS has not categorically denied Medicare reimbursement for routine costs in a Phase I Study
  - Local contractors may have issued statements, parse them through carefully
  - Ask forgiveness not permission, but do so with good documentation
- Oncology trials easier to document than non-oncology trials as cancer studies enroll patients with diagnosed disease in hopes of benefit while identifying MTD
- Challenges for Phase I
  - Studies designed to identify a maximum tolerated dose (MTD) as quickly as possible so that the study may move into Phase 2 and test the benefit.
  - Studies are designed with “dose-escalation” so that the subjects receive different doses of the drug in order to find the MTD. Goal (alone) is not benefit but to identify the toxicities and locate the MTD
  - Pushback from IRB related to overstatements of benefit and therapeutic misconception

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Operational Approaches

- “Early Phase Worksheet” that highlights TI:
  - Study enrolling subjects diagnosed with disease?
  - Is disease under study chronic, life threatening or debilitating?
  - Is trial intended to exclusively study toxicity and/or pathophysiology?
  - In what way does the protocol demonstrate TI? Listed in the primary, secondary and/or tertiary objectives? End points? Describe.
  - Will the medical record and/or research record document how the participants are progressing through the trial? If yes, describe criteria used to document progress.
  - PI Acknowledgment with explanation of significance of TI

* Derived from Worksheet from Cedars-Sinai Medical Center

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Operational Approaches

- Establish an Early Phase Review Committee
  - Staffed by PIs and AMC staff/research staff
  - Not typically IRB member
  - Develop Review Protocol seeking concurrence with PI's TI rationale
- Cite in the MCA the protocol objective or endpoint that evidences therapeutic intent

Questions