MD TIP Workshop II
Getting your innovative medical device to market:
Clinical Study Design Considerations

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Intended Objectives

- Identify the correct patient population
- Identify the appropriate control and study endpoints
- Determine the length of follow-up
- Understand the balance between premarket and postmarket requirements
- Understand the difference between clinical practice and participating in a clinical investigation
Common obstacles to device access

- Device may need to be studied clinically first
  - Valid scientific evidence
- Regulatory bar for Europe is different than for US
  - Safety only vs. safety & effectiveness
- FDA approval does not mean CMS coverage
  - Safe & effective vs. reasonable & necessary
  - Data is confidential vs. publicly available
The Basics

How do I get my innovative medical device on the market?
Safety

“There is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.”

21 CFR 860.7
Effectiveness

“There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

21 CFR 860.7
Valid Scientific Evidence

“The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations…”

21 CFR 860.7
Valid Scientific Evidence

Also evidence from:

- partially controlled studies,
- studies and objective trials without matched controls,
- well-documented case histories conducted by qualified experts, and
- reports of significant human experience with a marketed device from which it can be fairly and responsibly concluded by qualified experts that there is a reasonable assurance of safety and effectiveness

21 CFR 860.7
Least Burdensome

- Congress intended FDAMA to streamline the regulatory process…

…but not to lower the statutory basis for device clearance/approval
Least Burdensome Principles

- Leverage publicly available information and data from earlier generations
- Consider alternatives to RCTs when potential bias associated with alternative controls can be addressed
- Rely on post-approval studies when appropriate
Threshold of Evidence

- Bench data and/or animal data alone:
  - when there is confidence that the data is predictive of the clinical outcome
  - where bench data or animal data correlates with clinical data, i.e., you have validated your model

- Bench, animal and clinical data needed:
  - when there is not sufficient confidence that the preclinical data can predict clinical outcome
Basic Principles

- Early interaction
- Base conclusions on valid scientific evidence
- Characterize the device and its effects completely
- Measures used; 3 W’s: what does it tell us, what does it mean, why do we care?
- Look at the total picture
Have a Plan

Before you begin your pivotal clinical study…
Basic Considerations

- Device and material characterization
- In vitro and in vivo safety & performance
  - Proof of concept
  - Device interaction
  - Biocompatibility
  - Functional
- Manufacturing
  - Design Controls
  - Sterility
  - Stability
  - Shelf life
Phased Approach to Medical Device Development

- Pre-Clinical
  - Bench and Animal Studies
- Early Clinical
  - 1st in Humans, Feasibility or Pilot Studies
- Clinical to Support Market Entry:
  - One or more Pivotal Studies
- Post Market
  - MDRs
  - Postmarket Surveillance
  - Conditions of Approval Studies
  - 522 Studies
Animal Studies

Why are they needed?
Animal Studies

- Often critical to assess the best way of using the device prior to human use.
  - Gain experience with procedure or implantation technique.
- Optimize:
  - Location of implants
  - Number of implants
  - Dose of treatment
  - Treatment parameters or settings
Animal Studies (cont)

- Address short- and long-term safety issues.
  - Localized tissue reaction – histology often unethical in humans
  - Biocompatibility and toxicity of materials
  - Maximum tolerated “dose”
  - Types, severity, general rates of local (systemic) adverse events
  - Assess for modes of failure in an in-vivo model
Animal Studies (cont)

- Results of animal studies may lead to changes:
  - Device design
  - Device implantation technique
  - Device procedure
  - “Dosing” of device
- May support mechanism of action
- May suggest adverse events to observe in clinical trial
- May provide level of assurance of implant material safety.
Pilot Studies

Why do I want to start with a pilot?
Top 10 reasons for a pilot study

- Help address specific safety concerns
- Permit initial assessment of device design
- Better define/refine the clinical endpoints
- Establish appropriate assessment tools and success/failure criteria
- Provide investigators with initial device experience and identify special training needs
Top 10 reasons for a pilot study (cont)

- Determine the intended patient population
- Determine appropriate follow-up period
- Assess the therapeutic effect of the device
- Estimate the required patient population size
- Clarify the possible medical claims before the multi-centered trial is initiated.
Pivotal Clinical Study

What are the challenges?
Challenges

- Devices are different than drugs
- Use of OUS (outside US) clinical data
- Designing clinical studies in the setting of changing standard of care
- Use of surrogate endpoints
- Designing real-world trials
- Off-label use
- Postmarket studies
## DRUGS VS DEVICES

<table>
<thead>
<tr>
<th>Developmental Feature</th>
<th>Device</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of technology change</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ease of <em>in vitro</em> assessment</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Reimbursement during clinical trials</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
<tr>
<td>Influence of physician technique on results</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Ability to visualize performance after use</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Definition of “Orphan” (number of patients)</td>
<td>4,000</td>
<td>200,000</td>
</tr>
<tr>
<td>Number of full scale studies usually required</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Number of Regulatory Classes</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>
Use of OUS clinical data

OUS (foreign) clinical data can be used to support approval of medical devices in the US

Generalizability of OUS study results to the patient population in the US is a key issue

Sponsor must address the factors that may affect generalizability and justify why results are applicable to the US

- Patient demographic and clinical characteristics, geographic differences in medical practice, and differences in study protocol
Changing standard of care

- Move from superiority studies (new treatment vs. placebo) to non-inferiority studies (new treatment vs. currently approved treatment)
- Selection of clinically relevant delta (margin of non-inferiority)
- Concern for “outcome drift” with successive non-inferiority studies
Surrogate Endpoints

- Surrogate endpoints
  - Advantage is smaller scale outcome trials
  - Limitations
    - May not be validated as predictive for mortality
    - Determine clinically meaningful difference between treatment and control groups for evaluation of clinical benefit
- Single vs. combination of endpoints
Designing real-world trials

- Known limitations of most pre-approval studies
  - Well-defined population
  - Attempt to be representative but need strict inclusion/exclusion criteria
  - Genetic idiosyncracies not adequately tested
  - Operators usually most experienced in field

- Encourage creative approaches to include more “real-world” patients and clinical scenarios
Off-label use

What is “off-label use” according to the FDA?
- Use of a medical device for treatments other than for what the device was initially approved.
- Use not explicitly included in product labeling.
- Also referred to as “unlabeled,” “out-of-label,” “extra label” and “unapproved” use.

Why is it a concern?
- Not subject to a rigorous pre-market approval process.
- May diminish or eliminate the incentive to study
- Adverse events associated with off-label use may not be captured and analyzed; patients not informed properly
Postmarket Studies

- Intended to address long term questions of safety and effectiveness and/or capture rare but serious adverse events
- Cannot replace the basic safety and effectiveness data required for premarket evaluations
- Interpretation of results due to missing data is problematic
- Compliance is a problem
Study Design

What are the key features?
Key Features of Market Entry Study

- Statement of Intended Hypothesis
- Adequate sample size
- Intent to treat methodology
- Target population identified
- Success/failure and other key definitions defined
- Objective evaluation identified and scheduled
- Data collection tools defined
- Length of follow-up
Other important considerations

- Data and Safety Monitoring Board (DSMB)
- Clinical Events Committee (CEC) adjudication
- Use of core labs for independent analysis
Study Design

What are the drivers to a good study design?
Key factors that drive the study design

- Indications for use and diversity of the target population
- Standard of care
- Variability of device performance when used by practitioners with varying expertise
- Available alternatives
- Device risk profile

DRAFT Guidance “Design Considerations for Pivotal Clinical Investigations for Medical Devices”
Special Considerations

- Mechanism of action
- Principles of operation of the device
- User skill level and training
- Learning curve
- Human factors
Study Design

Bias and variability in device performance
Controlling for sources of bias

- The right data is more important than simply collecting more data.
- Bias is the introduction of systematic errors from the truth.
- Bias can distort the interpretation of study outcomes.
- Not reducing sources of bias may invalidate the final study results.
- Insufficient data on device effect may lead to device effect being overwhelmed by bias.
Sampling variability

- Controlled by the sample size
- Large studies provide more data so there is less variability yielding more precise estimates
- However large studies can result in clinically insignificant outcomes that show statistical significance
- Studies should be designed to show both clinical and statistical significance
Study Design

Selecting an appropriate control
Types of controls

- Concurrent
  - Active
  - Sham
  - No intervention
  - Subject as their own control (e.g., split face)
- Non-concurrent
  - Subject as their own control (baseline)
  - Historic control
Limitations of non-concurrent controls

- Use of baseline outcomes as comparison inadequate
  - Regression to the mean
  - Hawthorne effect
- Historical controls as comparison problematic
  - Severe and unknown selection bias
  - May not reflect current practice; temporal bias
  - Significant challenge with missing data
  - Endpoints may have been evaluated differently
Study Design

To Randomize or *Not* to Randomize…
Randomized Controlled Trials (RCT)

- Randomized controlled trials are the gold standard for evaluating new Device and Drug therapies
  - enhances likelihood that comparable groups of subjects are actually compared
  - reduces the likelihood of patient selection bias
  - supports use of common statistical tests
Common responses against RCT

- It’s not ethical
- People won’t sign up
- It costs more
- Less data on the subject device
- We already know it works better
Are there other options…

- Propensity Scores (PS)
- Objective Performance Criteria (OPC)
- Other alternative trial designs
Propensity Score Analysis

- Lack of randomization raises issues regarding comparability of patients in the different treatment arms due to baseline differences or covariates.
- By allowing for simultaneous adjustment for many covariates, “propensity score” (PS) analysis may be used to show comparability of the two groups.
Propensity Score Analysis (cont)

- Individuals are sorted based on their PS into a small number of equal-sized subclasses or “strata.”
- Within each stratum, the two groups are compared using the outcome measures.
- If two groups overlap well enough in terms of PS, then it is possible to check the influence of cohort effect on the outcome variable adjusted for baseline differences.
Propensity Score Analysis (cont)

Limitations

- Can only adjust for observed confounding covariates and not for unobserved ones.
- Cannot eliminate all selection bias
- Works better in larger samples
- Does not serve as a substitute for RCT
Objective Performance Criteria

- **Fixed Target**
  - Benchmark for minimally acceptable values
- **Surrogate for control group?**
- Driven largely by historical data
  - Requires appropriate pooling of different investigations
  - Inherit all problems seen with historical controls
    - May be too far removed in time
    - Tend to produce more positive results
Objective Performance Criteria (cont)

Advantages

- Allows for smaller sample size
- Sets standard value for all sponsors (level playing field)
- Saves time and money
- Easier to execute
- “Least burdensome”
Objective Performance Criteria (cont)

- Disadvantages to OPCs
  - Problems of historical controlled studies
  - Problems accounting for advancements in practice of medicine
  - Problems on agreeing to the final OPC value
  - Problems with selection bias
  - Resource intensive to develop the OPC
  - Statistical model does not allow for determination of superiority – just whether criteria is met or not.
  - Older and older data
  - What if OPC is not met but barely?
Objective Performance Criteria (cont)

- When would use of OPC be appropriate?
  - Great deal is known about the natural history of the disease or condition
  - Underlying patient population is well described and stable (not much variability)
  - Extensive clinical history and experience with the device type.
  - Stable and well-known S.O.C.
  - Ancillary technology is stable
  - Consensus among FDA, industry, clinical communities
Other Alternative Trial Designs

- Any study that deviates from the gold standard, i.e., RCT
- Agency is open to alternatives when
  - Scientifically sound
  - Addresses the relevant safety and effectiveness questions
Case Studies

Combination Products
Device + Drug = Cancer Tx

- Using a medical device to enhance the delivery and targeting of a drug
- What is the primary mode of action?
- What is the standard of care?
- What is the drug approved for?
- What could be all the contributing factors?
Device + Drug = Cancer Tx

- Must identify the specific drug to be used
- Drug and Device must have mutually conforming labeling by Law
- Treatment effect may come from the drug alone, the device alone, or a combination of the two
- Drug is labeled for IV injection
- Treatment is localized
- Device increases the absorption of the drug
Case Studies

Localized Prostate Cancer
Ten year multicenter randomized clinical trial (RCT) of patients with localized prostate cancer

Assessment of a new therapy to the current standard of care
Study Objectives

- Determine if a new therapy is superior to current standard of care with respect to the proportion of patients that remain disease free, i.e., progression free PSA in accordance with ASTRO criteria, over 10 years.
Prostate Cancer

- 4th most common male malignancy worldwide
- Worldwide and ethnic variation of incidence and mortality rates
- Long natural history in disease progression
PCa Incidence in US by Age

1SEER data from NCI reported in Campbell’s Urology, 2002
Prostate Specific Antigen (PSA)

- 33 KD protein of the family of serine proteases.
- Secreted by epithelium of the prostate and peri urethral glands
- Not tissue or gender specific but serum PSA w/benign & carcinoma cells can be used as organ specific marker
- 2 forms: free (30%) and complex (70%)
Current Tx for localized PCa

- Std of care in US
  - Watchful waiting
  - Radical Prostatectomy
  - EBRT
  - Brachytherapy
  - Cryotherapy*

- Emerging Tx
  - HIFU
  - Thermo Therapy
  - Rods
  - Microwave
  - Photodynamic therapy
  - Other

*Limited adoption of this therapy in U.S. due to lack of long-term data
Biochemical disease-free survival of current therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>10 yrs Survival</th>
<th>15 yrs Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful waiting</td>
<td>~83%</td>
<td>89-96%</td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>~76%</td>
<td>83%</td>
</tr>
<tr>
<td>EBRT</td>
<td>~76%</td>
<td>83%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>66-85%</td>
<td>89-96%</td>
</tr>
</tbody>
</table>
Clinical Prognostic Factors

- Clinical Stage (tumor-node-metastasis (TNM) system)
- Prostate Specific Antigen (PSA)
- Biopsy Gleason Grade
Inclusion Criteria

- Adult men > 50 years of age
- T1a, b, c, and T2a stage prostate cancer
- PSA <10 ng/ml
- Positive biopsy with Gleason score ≤ 6.0
- <30% of positive cores from 1 lobe using std sextant TRUS PBx
- Life expectancy >5 years
Exclusion Criteria

- Confounding medical history, e.g.,
  - tx of the prostate
  - compromised renal function
  - suspect bladder pathology
  - rectal surgery, etc.

- Urological complications w/in 3 mos., e.g.,
  - hematuria, strictures
  - acute prostatitis
  - urinary retention
  - PVR > 500 ml, etc.

- Concerns of future fertility

- Alternative therapies w/in 6 mos., e.g.,
  - antiandrogen
  - LH agonist therapy
  - radiation
Control

- Watchful waiting
- Radical Prostatectomy
- EBRT
- Brachytherapy
- Cryotherapy*
Endpoints

- **Primary**
  - progression free as confirmed by PSA
  - negative biopsy at 12 months post nadir
  - safety profile of AE/complications

- **Secondary**
  - validated QOL measure of overall health as well as measures for urinary, sexual, and bowel functions
  - I-PSS
  - maximum voiding flow rate >12ml/sec
Statistical Analysis

- Repeated Measures annually over 10 yrs of the proportion of patients bNED:
  - Ho: p0 > p1  $\alpha=0.05$
  - Ha: p0 $\leq$ p1  $\beta=0.10$

- Assumptions: normal distribution, normal approximation valid, categorical and continuous outcomes

- Contingency plan: exact methods or non-parametric methods
Success Criteria and Effect Size

- Success is defined as bNED in accordance with ASTRO
- Assume brachytherapy has an expected success rate of 80% and the new treatment an 85% success
- \( p_0 = 0.80, q_0 = 0.20, p_1 = 0.85, q_1 = 0.15 \)
- Assume a 2-sided test using z-scores
- \( N = 515 \)
- Attrition is expected to be high so if we assume 5% every year we could lose as many as 260 patients over 10 years so at least 775 patients are needed
Other Analyses

- ANOVA
- Significant Covariates
  - Age
  - Heredity
  - Prostate size
  - Confounding meds
  - Significant comorbidities
  - Gleason score
  - Ethnicity
  - Diet
Case Studies

Prostate Cancer: focal vs whole gland
Focal Therapy

- Is it a flexible option or suboptimal treatment?
- What is the appropriate control?
- What is the length of follow-up?
- What is the appropriate risk benefit?