Examining the Role of Patient Preferences to Inform Regulatory Decisions

Third Plenary Session

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Q&A

THIRD PLENARY:
Examining the Role of Patient Preferences to Inform Regulatory Decisions

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The Role of Patient Preferences to Inform Regulatory Decisions

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Patients are at the Heart of What We Do

CDRH Vision: Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world

Medical Device Total Product Life Cycle

Device Benefit-Risk Frameworks

Factors to Consider for Benefit – Risk Determinations Medical Device Premarket Approval and De Novo Classifications

Medical Device Benefit-Risk Guidance

Factors to Consider Regarding Benefit-Risk in Medical Device Product Development and Innovation

Patient Perspectives

• Information relating to patients’ experiences with a disease or condition and its management
  • May be useful for:
    -- better understanding the disease or condition and its impact on patients
    -- identifying outcomes most important to patients
    -- understanding benefit-risk tradeoffs for treatment

Patient Perspective Studies

Patient Preference Information (PPI)

Patient Reported Outcomes (PRO)

Patient perspective on tradeoffs of benefit and risk:

Example: Glaucoma and Macular Edema

Health status: symptoms, function, quality of life reported from the patient without input from anyone else

Examples:
  -- Questionnaires
  -- Rating scales
  -- Patient diaries

www.fda.gov
What is Patient Preference Information?

- Patient Preference Information (PPI) is defined as:
  - Qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions.

- Relevant preferences of care-partners (e.g., parents) and health care professionals may also be considered.

Patient Preference Information (PPI)

- Qualitative PPI may be used to:
  - Identify which outcomes, endpoints or other attributes are valued most by patients.
  - Understand which factors affect patients’ perspectives on risk and benefit.

- Quantitative PPI may be used to:
  - Provide estimates of how much different outcomes, endpoints or other attributes are valued by patients.
  - Understand tradeoffs that patients state or demonstrate they are willing to make.

Complementary Efforts

<table>
<thead>
<tr>
<th>Benefit-Risk Dimensions</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDER FOCUS</td>
<td>Evidence of Clinical Benefit</td>
<td>Conclusion that supports benefit over risk considerations</td>
</tr>
<tr>
<td>CDER PPI</td>
<td><strong>Evidence of Clinical Safety</strong></td>
<td>Conclusion that supports risk considerations</td>
</tr>
<tr>
<td>CDRH FOCUS</td>
<td>Evidence of Clinical Efficacy</td>
<td>Conclusion that supports efficacy considerations</td>
</tr>
</tbody>
</table>

PPI in Medical Product Development

<table>
<thead>
<tr>
<th>Development</th>
<th>Clinical Trial/Design</th>
<th>Pre-Market</th>
<th>Post-Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identify what matters most to patients about their disease or treatment.</td>
<td>1. Identify endpoints that matter most to patients.</td>
<td>1. Inform endpoints selection.</td>
<td>1. Infrom interpretation of new data affecting benefit-risk assessment.</td>
</tr>
<tr>
<td>2. Understand what matters most to patients about their disease or treatment.</td>
<td>2. Inform performance goal.</td>
<td>2. Inform performance goal.</td>
<td>2. Inform new data affecting benefit-risk assessment.</td>
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</tbody>
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Medical Device Patient Preference Initiative

Patient Preference Guidance

Patient Preference Information — Voluntary Submission, Review in PMAs, HDE Applications, and De Novo Requests and Inclusion in Decision Summaries and Device Labelling

Objectives

1. To encourage submission of PPI, if available, by sponsors or other stakeholders to FDA and to aid in FDA decision-making.
2. To outline recommended qualities of patient preference studies, which may result in valid scientific evidence.
3. To provide recommendations for collecting and submitting PPI to FDA.
4. To discuss FDA’s inclusion of PPI in its decision summaries and provide recommendations for the inclusion of such information in device labeling.
**PPI as Valid Scientific Evidence**

- FDA may consider submitted PPI along with other evidence from clinical and nonclinical testing when making benefit-risk determinations.
- This guidance does not change any review standards for safety or effectiveness.
- It provides recommendations relating to the voluntary collection of PPI that may be submitted for consideration as valid scientific evidence as part of FDA's benefit-risk assessment.

**Recommended Qualities of Patient Preference Studies**

Well-designed and conducted patient preference studies can provide valid scientific evidence regarding patients’ risk tolerance and perspective on benefit. This may inform FDA’s evaluation of a device’s benefit-risk profile during the PMA, HDE application, and de novo request review processes.

- **A. All about Patients**
  - Patient Centricity
  - Sample Representativeness
  - Capturing Heterogeneous Patient Preferences
  - Comprehension by Study Participants
- **B. Good Study Design**
  - Established Good Research Practices
  - Effective Benefit-Risk Communication
  - Minimized Cognitive Bias
  - Methodology
- **C. Good Data Collection and Analysis**
  - Study Conduct
  - Logical Sarcasm
  - Robustness of Analysis of Results

**Lessons Learned from PPI Reviews**

- Consult FDA early in designing PPI studies for a regulatory context.
- Ensure PPI benefit and risk attributes match to outcomes of interest in clinical studies.
- Pre-test instrument to ensure patient comprehension of benefit, harm, and uncertainty.
- Develop a plan for recruiting patients:
  - Ensure there is heterogeneity and generalizability of the study sample
  - Take into account recruiting for underserved populations
- Pre-specify analysis plan and potential subgroups.

**PPI Submission to FDA is Voluntary**

- PPI may not be relevant or appropriate for all device types.
- May be useful for sponsors to collect and submit such information where usage decisions by patients and health care professionals are preference-sensitive.
- Devices that could benefit from PPI include those with the following characteristics:
  - A direct patient interface
  - Intended to yield significant health and appearance benefits
  - Intended to directly affect health-related quality of life
  - Certain life-saving but high-risk devices
  - Developed to fill an unmet medical need or treat a rare disease or condition
  - Offer alternative benefits to those already marketed
  - A novel technology.

**Regulatory Impact**

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Advancing the Science

- Understand which methods are fit-for-purpose for the following types of questions:
  - Regulatory benefit-risk tradeoffs
  - Endpoint identification and/or prioritization
  - Identifying outcomes to guide patient-reported outcomes development
  - Informing clinical trial size

- Develop and refine approaches for:
  - Cognitive bias minimization
  - Effective communication of benefit-risk information to patients
  - Qualitative research best practices
  - Evaluation of study and data quality

Advancing the Science (Continued)

- Need to build capacity
  - Develop and establish training programs
  - Research resources and tools
  - Establish the value proposition for various regulatory uses

- Should include:
  - Sharing findings publicly
  - Establishing good work and good data collection tools for others to use or build on
  - Contributing to establishing standards regarding study quality and validity

Final Considerations

- FDA is invested in including the patient perspective in regulatory decision making
- ISPOR and other professional organizations can help advance the science of patient input by addressing existing scientific questions about robust and reliable preference studies, through:
  - Building capacity for conducting and assessing PPI studies
  - Methodology research to overcome current barriers to conducting and incorporating PPI studies to inform regulatory decision-making
- We are all working to do more research to strengthen the approaches for greater quality, trust, cost efficiency, and respect for patients’ views and time

Thank You

THIRD PLENARY: Examing the Role of Patient Preferences to Inform Regulatory Decisions

Jeff Shuren, MD, JD
U.S. Food and Drug Administration (FDA)
Silver Spring, MD, USA
THIRD PLENARY: Examining the Role of Patient Preferences to Inform Regulatory Decisions

My views on stated preference methods via a tour of my music collection

Matt Reaney, Global Head of Clinical Outcomes
May 23 2018

Disclaimer
The views expressed in this presentation are my own and do not necessarily reflect those of Sanofi.

- Patient Preference Information (PPI) can be extremely relevant
- Identifying what is important, desirable or valuable to patients can be important for sponsors
  - TPP
  - Trial design
- Particularly relevant where benefit-risk trade-off is not clear, or where a novel route/mode/frequency of administration is under consideration
- Also very relevant in a choice-based healthcare system

“You can’t always get what you want, but if you try sometimes you might just find you get what you need”

My issues with stated preference methods to allow regulatory judgement about benefit-risk of a drug, device or biologic

“I tried to think of the most harmless thing… Something that could never, ever possibly destroy us”
"I tried to think of the most harmless thing... Something that could never, ever possibly destroy us"

However, there is a conflict between stated preferences and ‘patient experience’

- attitudes vs expectations vs intentions vs actual behaviour
- In hypothetical (decontextualized) situations:
  - People use decision-making heuristics to “project”
  - Diminished role of normative beliefs
  - Emotion not accounted for

“Reliability and validity of stated preference data questionable”

- Validity:
  - Assume health literacy/numeracy
  - Comprehensiveness
  - Cognitive overload / information bias
  - Order effects / interdependencies

- Reliability:
  - Internal consistency questionable
  - Cognitive reframing
  - Desirable responding
  - Subjective norm

Generalisability
Reliability and validity of stated preference data questionable

Validity:
- Assume health literacy/numeracy
- Comprehensiveness
- Cognitive overload / information bias
- Order effects / interdependencies

Reliability:
- Internal consistency questionable
- Cognitive reframing
- Desirable responding
- Subjective norm

Generalisability

"How infinite is space and who decides your fate; Why everything will dissolve into sand….Why nothing ever turns out as you plan; These are things that I don’t understand"

"I would like to dive for pearls, but the water's way too deep"

The Self-Regulation Model

Evaluation

Intention

Scale

Plans

Behaviour

Outcomes

Subjective and Objective

Emotions

Social Support and Pressure

Proxies for preference
- Satisfaction
- Patient-perceived benefit-risk

Patient preference information in routine clinical practice a cornerstone of EBM

Regulatory use of stated preference methods cannot do:
- Tell us about patient experience
- Tell us about satisfaction/acceptability
- Replace other research
- Inform us about decision making under “real life” circumstances
  - Maximum acceptable risk?
  - Minimum acceptable benefit?
- Provide a global comparison (embedding effect)
- Tell us why things are important

Regulatory use of stated preference methods:
- Label should include patient experience data.
- Experience-based preference evaluation could be included in labelling
  - equal exposure to two treatments is required
  - or at least experience in previous lines
- Proxies for preference
  - Satisfaction
  - Patient-perceived benefit-risk

Patient preference information in routine clinical practice a cornerstone of EBM

"There’s still time to change the road you’re on"

Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular non-Hodgkin’s lymphoma (FL) Grades 1, 2, or 3a were randomized to receive a standard chemotherapy regimen (CHOP, CVPP, or bendamustine) and either RITUXAN Hyclara 1,400mg-2,400mg at Cyclces 2-4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cyclces 1-4. After the fourth cycle, patients were counselled over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 629 patients (78%) reported preferring subsequent administration of RITUXAN Hyclara over intravenous rituximab and the most common reason was that administration required less time in the chair. After Cycle 8, 66 of 629 patients (11%) preferred intravenous rituximab administration and the most common reason was that it felt more comfortable during administration. Forty-eight of 629 patients (7.7%) had no preference for the route of administration. Forty-nine out of 629 patients (7.7%) received Cycle 8 but did not complete the preference questionnaire.

"There’s still time to change the road you’re on"
If strong preferences are observed, this may undermine the credibility of the RCT if comparison is preference-sensitive.

Recruitment
Retention
Behaviour modification
- Trial outcomes = function of treatment +/-
  - Motivation
  - Adherence
  - Expectations

"It keeps holding on; And it's holding strong; Even though I tried to break it; Heaven knows that I can't shake it"

Patient Preference Information (PPI) to be used:
- Sponsor:
  - Identifying outcomes of interest
  - Determining commerciability
  - Trial design
- Decision-makers
  - Regulators; to inform B-R decision-making
  - Payers; reimbursement for choice
  - Prescribers; individual-PPI

But I still haven't found; What I'm looking for"

Regulatory considerations of PROs: which would enhance stated PPI:
- Content validity
- Context of Use
- Test-retest (internal validity)
- Interpretability (meaningful) responses
- Interdependencies
- Comprehensiveness
- Cognitive reframing
- Cognitive overload
- Desirable responding
- Subjective norm
- Generalisability
- Missing data

"Lean on me when you're not strong and I'll be your friend; I'll help you carry on"

"Stop right now; Thank you very much"
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Structured Benefit-Risk: B-R Frameworks

- Set of principles, guidelines and tools for selecting, summarizing and communicating evidence for B-R decisions
- Preference can inform many elements common to all frameworks

FDA/B-R Framework

- PHRMA BRAT Framework

EMAPROACT-URL

Considerations for Patient Preference Studies to Inform Regulatory Decisions

ISPOR 2018 Meeting
May 23, 2018

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Department of Epidemiology
Janssen Research & Development, LLC

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Janssen Research & Development
Titusville, NJ, USA
Three Types of Patient Preference Information

<table>
<thead>
<tr>
<th>Type</th>
<th>What it Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributes</td>
<td>What Matters</td>
</tr>
<tr>
<td>Relative Importance</td>
<td>How much it matters</td>
</tr>
<tr>
<td>Tradeoffs</td>
<td>What tradeoffs patients are willing to make between benefits, harms, and other aspects</td>
</tr>
</tbody>
</table>

Adapted from RTI-HS and MDIC

Which endpoints do patients care about? Example: Fragile-X Syndrome

- Rare genetic condition impacting development
  - Learning and intellectual disabilities, cognitive impairment, behavioral challenges (ADHD, autism, social anxiety)
  - No cure – educational, therapeutic support
- Preference study conducted to prepare for phase 3 study
  - Intent was to identify which endpoints or components of existing instruments were most important to patients
  - Survey administered to family members, given patient cognitive limitations

Preference Survey Identified Large Gap Between Clinician and Patient Caretaker Beliefs on Endpoint Importance

Preferences Supporting B-R in FDA Advisory Committee Atrial Fibrillation Example (mock data)

Identifying Differences Between Key Stakeholders

Preferences for Anticoagulants in Atrial Fibrillation

US Physician vs US Patient
What Sponsors Worry About When Considering A Patient Preference Study

- Do we really need it?
- Validation?
- Will regulators pay attention?
- Can it go in the label?
- How rigorous?
- What method?
- When should we do it?
- Work with a patient group?
- Can patients do it?
- How much does it cost?
- Whose preferences?
- Representative/Generalizable?
- Who can help us?
- How long will it take?
- Can we trust the results?

Patient Experience Section included in Rituxan Hycela Label (Approved 2017)

Several Classes of Preference Elicitation Methods

- Discrete Choice Based
- Threshold related
- Rating related
- Ranking related

Variety of similar techniques within each class

Growth of Regulatory Expectations, Guidance and Initiatives in Patient Engagement, B-R, and Patient Preferences

Approaches to Address These Concerns – selected examples

Survey Development

- Use good research practices guidelines
- Focus on the research question (keep it simple)
- Qualitative interviews/studies before (bottom-up approach)
- FDA’s open approach – early discussions and protocol review
- Consortia approach
- Fund larger, more representative samples
Focus the Preference Survey on the Research Question

Factors influencing whether patient preference information may be valuable for regulatory review

<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients and stakeholders</td>
<td>Patients' benefit-risk preferences differ from providers or regulators. Patient preferences with different preferences would make different decisions.</td>
</tr>
<tr>
<td>Benefit-risk trade-offs (preference sensitive)</td>
<td>Benefits are not obvious (e.g. clear benefit with rare serious side effects). Time separation of benefits and harms. Considerable uncertainty about benefits and harms.</td>
</tr>
<tr>
<td>Regulatory novelty</td>
<td>Lack of regulatory precedent for population or indication New technologies in existing area or existing technology in a new area.</td>
</tr>
</tbody>
</table>

Two approaches to developing patient preference studies

- **Product-evaluation (top-down) approach**
  - Disease and preference experts define features and priorities
  - Often applies to existing products/services or those in development
  - Survey prototyped similar to cognitive debriefing
  - Example: CDRH weight-loss preference study (Ho et al., 2015)
  - Typically faster and less expensive

- **Issues-identification (bottom-up) approach**
  - Patients define relevant features, priorities and need in qualitative interviews
  - Not necessarily specific to the features of an existing product
  - Survey development similar to concept elicitation
  - Example: PPMD Duchenne Muscular Dystrophy Studies (Hoit et al., 2015; Peay et al., 2014)
  - Typically takes more time and funds

Two approaches to developing patient preference studies

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Potential Internal Validity Tests

- Repeat questions
- Elapsed time
- Dominated pair (mostly DCE)
- Straight-lining or patternning (e.g. all column A)
- Domination (always deciding based on a single attribute)
- Monotonicity tests
- Translivity tests
- Scope tests (check for recoding of levels)
- Face validity
- Internal consistency (variance) of a subject’s utilities

Approaches to Address These Concerns – selected examples

<table>
<thead>
<tr>
<th>Survey Development</th>
<th>Survey Testing</th>
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<tr>
<td>Use good research practices guidelines</td>
<td>Pretesting</td>
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<td>Qualitative interviews / studies before (bottom-up approach)</td>
<td>Internal validity tests</td>
</tr>
<tr>
<td>FDA’s open approach – early discussions and protocol review</td>
<td>Pilot survey</td>
</tr>
<tr>
<td>Consortia approach</td>
<td></td>
</tr>
<tr>
<td>Fund larger, more representative samples</td>
<td></td>
</tr>
</tbody>
</table>

Multiple Methods

**BWS vs. DCE, Type 2 diabetes treatments**

*Results: Mixlogit (rho = 0.89)*

**BWS** = best-worst scaling
**DCE** = discrete choice experiment

Janssen, Segal and Bridges, The Patient, vol 9, issue 5, 2016

BWS = best-worst scaling
DCE = discrete choice experiment
Sample Source – Can be very important to use more than one – ex: panels vs. RCTs

**On-line Panel**
- Advantages:
  - Many options readily available in many countries
  - Generally inexpensive
  - Can perform probabilistic sampling to match basic criteria
- Concerns:
  - Self-report
  - Can be challenging to meet some inclusion/exclusion criteria
  - Limited associated clinical data
  - Selection bias – those who join on-line panels

**Randomized Clinical Trial**
- Advantages:
  - Trusted diagnoses and history
  - Associated clinical data
  - Longitudinal sampling
  - Health authority focus on work
  - Revealed choice by dropouts
- Concerns:
  - Many regulatory and legal requirements
  - Huge management overhead
  - ePRO vendor limitations
  - Huge increase in cost
  - Differs from real-world patients
  - Selection bias – those who choose to enter RCTs

Approaches to Address These Concerns – selected examples

**Survey Development**
- Use good research practices guidelines
- Focus on the research question (keep it simple)
- Qualitative interviews / studies before (bottom-up approach)
- FDA’s open approach – early discussions and protocol review
- Consortia approach
- Fund larger, more representative samples

**Survey Testing**
- Pretesting
- Comprehension tests
- Internal validity tests
- Pilot survey

**Repetition**
- Repeat survey in a new sample
- Used different sample sources
- Conduct survey with more than one method

**Post-Survey**
- Terminal questions (easy to understand, answers consistent with my preferences, relevance of vignette and attributes, etc.)
- Compare to other patient experience data
- Subject interviews (“why?”)
- Sanity tests (“Do the results make sense”)

A Goal for Preference Studies

agree on facts
Understand values

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