Understanding Benefit-Risk Assessment in Medical Product R&D

Objective: Describe how benefits and risks are assessed by pharmaceutical companies and regulators as a product is being developed, during clinical trials, and across the life cycle for approved therapies.
speakers

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Lifecycle-Based Benefit-Risk Assessment: An Overview

FasterCures Benefit-Risk Boot Camp
September 23rd, 2014

Robert Metcalf, PhD
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Lifecycle Benefit-Risk Assessment

Benefit-Risk – High Level

Benefit-Risk in Drug Development

Role of Patients in Lifecycle Benefit-Risk
The Critical Question

To be approved for marketing, a drug must be **safe and effective** for its intended use.

Across the lifespan of a drug, we ask one fundamental question...

Do the benefits of the drug exceed the risks for the indication and its expected use?

This benefit-risk assessment is the basis of pre-market and post-market regulatory decisions.
A benefit-risk framework is a systematic, consistent, and transparent approach (process and tools) that guides the assessment.

Historic reliance on expert judgment has many recognized challenges (e.g., consistency, transparency, reproducibility).

Structured benefit-risk assessment uses the concept of quality decision-making via frameworks.

Safety of a drug is assessed by whether its benefits outweigh its risks, but just how do we make that determination?
Value of Benefit-Risk Frameworks

Enriches (not substitutes for) human decision-making

• Tools and structured processes for selecting, organizing, interacting with, summarizing, and communicating data relevant to benefit-risk decisions

Improved knowledge management

• Maintain focus in light of the exponential increase in data volume and complexity

More effective communication and contextualization of benefit and risk

• Succinct, meaningful communication
• Incorporation of other perspectives (patients, caregivers, HCPs)

Outcome: Better drug/device development and post-marketing risk management
Drug Development Lifecycle: Benefit-Risk

The Standard Development Process
Starts from Clinical Planning Through Life Cycle Management

Phase 1-2: Demonstrate Clinical Proof of Concept
- Candidate selections
- Phase 1/2 Protocols

Phase 3: Registration Trials
- Dev Decision
- Reg Briefing Docs
- Product Labelling
- PBRERs
- Advisory Cmte

Regulatory Review & Approval
- Phase 3 Protocols
- Marketed Medicines Life Cycle Management
- REMS, PMRs/PMCs
- PM Surveillance

Market Applications
Example #1: End Of Phase 2 Structured Benefit-Risk Assessment

Benefit-risk assessment is performed to decide if a drug candidate should move forward into Phase 3.

• The decision to invest in Phase 3 is complex and involving multiple considerations:
  • Safety and Efficacy
  • Advantage over standard of care
  • Understanding of possible alternatives, potential development tradeoffs, and what treatments stakeholders value.
Structured Benefit-Risk to Address End of Phase 2 Key Questions

- Considerations raised with the development team:
  - Further characterization of the unmet medical need and the patient population, including relevant subgroups
    - What is the disease burden?
    - Is the further reduction in risk clinically meaningful and important to patients?
  - Clarification of how the drug will differentiate itself from similar treatments
    - Are patients interested in an “add-on” disease treatment?
- Using a structured benefit-risk approach enabled more robust decision-making by the development team
Example #2: Post-Marketing Benefit-Risk Assessment – PBRERs

The Periodic Benefit-Risk Evaluation Report (PBRER) presents a comprehensive and critical analysis of new or emerging information on risks and benefits of marketed products to enable an appraisal of overall benefit-risk.

Contains an evaluation of new, relevant information that became available to the drug sponsor during the reporting interval:

- Examines whether new information is in accord with previous knowledge of the benefit-risk profile.
- Summarizes relevant new safety, efficacy, and effectiveness information that may impact the benefit-risk profile.
- Presents an integrated benefit-risk evaluation.
Using Structured Benefit-Risk For PBRER Assessments

• Regulator assessment request for a marketed product in light of recent publications suggesting a potentially important safety signal for the drug.

• Content from the PBRER was leveraged to respond to the regulator’s request, including:
  • The disease burden.
  • Key benefits and key risks of the drug.
  • Strengths and limitations of evidence supporting key benefits and risks.
  • Ability to manage key risks.

• Using the structured benefit-risk assessment approach, the team assessed the impact of the potential safety signal, concluding no change to the benefit-risk balance.
Patients living with a disease have a direct stake in drug development and regulatory review processes. They are in a unique position to contribute to drug development.
Patient-Focused Input into the Benefit-Risk Framework

The previous slides illustrated just a few of the places where drug developers and regulators are incorporating structured benefit-risk assessment into the lifecycle.

Core Benefit-Risk Framework

1. Define development frame
2. Identify benefit and risk attributes
3. Collect, integrate, and summarize benefit & risk data
4. Interpret data and ascertain benefit-risk profile

PATIENT input contributes to shaping the benefit-risk process across the lifecycle.
Defining the development frame well requires consideration of the following issues from the patient perspective:

- How do patients experience the severity of their condition?
- What is the impact of the condition on patients and/or caregivers?
- Which clinical manifestations are of the greatest concern to patients?
- What are the benefits and risks of alternative therapies?

Identifying benefit and risk attributes requires an understanding of:

- Which benefit outcomes are most important to patients?
- Which risks are most concerning to patients?
- How much risk patients are willing to tolerate?
Define development frame

Identify benefit and risk attributes

Collect, integrate and summarize benefit & risk data

Interpret data and ascertain benefit-risk profile

Use of improved and enhanced technology to collect robust data with minimal burden to the patient

Interpreting data and ascertaining the benefit-risk profile requires:

• An understanding of which benefits and risks patients value most
  ✓ What are the best ways to gather representative patient input?

• Developing risk minimization programs responsive to patient preferences

• Developing user-friendly clinician and patient summaries of benefit-risk information
  ✓ How useful is label information to patients?
  ✓ What else do patients want and need to make more informed decisions?

Core Benefit-Risk Framework
Future Direction: Enhancing Patient-Focused Drug Development Input into Structured Benefit-Risk Assessments

• Both drug development and regulatory review could benefit from a more systematic and coordinated approach to obtaining the patient perspective.

• How do we best incorporate patient input into structured benefit-risk assessment?
  • Excellent start with PFDD, but how do we go further?
  • Need to advance PFDD by focusing on the “Science of Patient Input”.
    • Move from the era of the testimonial to the era of patient preferences by building robust, representative data via pre-competitive collaboration.
Lifecycle Benefit-Risk Assessment: A Big Win for Patients

Lifecycle benefit-risk assessment strengthens drug development and regulatory review, resulting in better therapies for patients!
Benefit-Risk Assessment: Early and Late Phase Development

Rebecca (Becky) Noel, DrPH, MSPH
Director, Benefit-Risk Assessment
Eli Lilly & Company
Benefit-Risk Decision-Making
Models for Decision-Making?

A good leader uses a process for making decisions.

May I take this one?

Make us proud.

Question: If making a decision is just a process, why can't a computer do it?

Because sometimes I have to rely on my gut.

Which part of your gut is the smart part? Is it the stomach lining, or maybe the colon?

I'm talking about instinct. It's an indefinable leadership quality.

Is the indefinable thing like a superstition?

Or cooties?

It's a process!

Is that your colon talking?
Structured Benefit-Risk Assessment: The Benefit-Risk Framework

Structured benefit-risk assessment uses the concept of quality decision-making via the use of decision analytic framework principles.

Frameworks provide systematic, consistent, and transparent process and tools to perform and communicate an assessment.
B-RA Frameworks: Support for Decision-Making and Communication

**FDA**

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<tbody>
<tr>
<td>Analysis of Condition</td>
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<td>Current Treatment Options</td>
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<td>Benefit</td>
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<td>Risk</td>
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<tr>
<td>Risk Management</td>
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**EMA**

- Favourable effects
- Uncertainty of favourable effects
- Unfavourable effects
- Uncertainty of unfavourable effects

**PhRMA BRAT**

**Table 1: Steps in applying the BRAT Framework**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>1. Define the decision context</td>
<td>Define drug, dose, formulation, indication, patient population, comparator(s), time horizon for outcomes, perspective of the decision makers (regulator, sponsor, patient, or physician)</td>
</tr>
<tr>
<td>2. Identify outcomes</td>
<td>Select all important outcomes and create the initial value tree. Define a preliminary set of outcome measures/end points for each. Document rationale for outcomes included/excluded</td>
</tr>
<tr>
<td>3. Identity and extract source data</td>
<td>Determine and document all data sources (e.g., clinical trials, observational studies) Extract all relevant data for the data source table, including detailed references and any annotations, to help the subsequent interpretations create summary measures</td>
</tr>
<tr>
<td>4. Customize the framework</td>
<td>Modify the value tree on the basis of further review of the data and clinical expertise. Refine the outcome measures/end points. May include tuning of outcomes not considered relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder group</td>
</tr>
<tr>
<td>5. Assess outcome importance</td>
<td>Apply or assess any ranking or weighting of outcome importance to decision makers or other stakeholders</td>
</tr>
<tr>
<td>6. Display and interpret key benefit-risk metrics</td>
<td>Summarize source data in tabular and graphical displays to aid review and interpretation Challenge summary metrics, review source data, and identify and fill any information gaps Interpret summary information</td>
</tr>
</tbody>
</table>

BRAT = B-R action team; EMA = European Medicines Agency; FDA = Food and Drug Administration; PhRMA = Pharmaceutical Research and Manufacturers of America
Multiple Frameworks but Common Concepts

- **Frameworks demonstrate**
  - Logical soundness
    - Coherent approach that aids rational thinking & judgment
  - Consistency
  - Practicality
  - Transparency

- **Systematic, qualitative approaches**
  - Decision aids to structure the evaluation:
    - Which benefits and risk were considered most relevant?
    - What was the evidence? How was the evidence interpreted?
    - What were the strengths, limitations and uncertainties related to the evidence?
    - How were the benefits and risks weighed or prioritized?
    - What can be done to manage and mitigate the risks?
      To optimize the benefits?

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Core B-R Process

- Define development frame
- Identify benefit and risk attributes
- Collect, integrate and summarize benefit & risk data
- Interpret data and ascertain benefit-risk profile
Multiple Frameworks but Common Concepts

- **Use of a “decision context”**
  - Recognition that benefit–risk assessments are dependent on:
    - Indication and severity of the condition
    - Umet medical need
    - Population(s) being treated
    - Other available treatments
    - Perspective (e.g., regulator, sponsor, patient, clinician)

- **Assessing outcome importance**

- **Visualizations: evaluating, summarizing, and communicating data relevant to the decision**
  - Attribute tree
  - Effects tables
  - Key Benefit-Risk Summary Table

- **Tracking and communicating uncertainties**

- **Communicating the decision rationale**
Drug Discovery and Development Process

- Target Identification and Validation
- Assay Development
- Lead Generation
- Early Phase I
- Late Phase I and Phase II
- Phase III
- Submission and Approval
- Marketed Product
- Hypothesis Generation
- Candidate Development
- Commercialization
Early Phase I Development

Compound is first administered in low, single doses to a small group of healthy volunteers.

Once tolerable single doses are determined, multiple administrations at those doses follow.

Purpose of this phase is to determine:

• Metabolic and pharmacologic actions of the drug in humans
• Side effects associated with increasing doses, and,
• If possible, gain early evidence on effectiveness
Late Phase I to Phase II Development

Drug is administered to a relatively small number of patients to determine efficacy and safety (known as proof of concept).

Once an effective and safe dose is determined (dose-response), other studies are done to determine appropriate dosage and schedule to take forward into larger trials.
Phase III Development

Phase 3 trials test the results of earlier trials in much larger groups of people while gathering additional effectiveness and safety information.

- Involves hundreds to thousands of participants.
- Use randomization to allocate patients to experimental therapy, placebo or another (comparative) therapy.
- Generally provides the primary basis for the benefit-risk assessment for the new therapy and much of the core information about the therapy.
Some uncertainties in early development include:

- **Expected effect size** (treatment related effects)
  - Small sample sizes, study length
  - Changes in study design between phases may alter the relevance of early phase data
- **Limited safety information**
- **Endpoint selection and refinement**
  - Translation from preclinical to humans
  - Several types of measures can be used for the same objective
  - May require varying assessment approaches
Benefit-Risk Considerations in Early Development: Value

• Alignment on the development frame
  ✓ Early consideration of appropriate comparators, time horizon, exact patient population, risk minimization

• Identification and consideration of benefit and risk attributes, especially from the patient perspective
  ✓ Risk tolerances and preferences
  ✓ Beyond efficacy endpoints, consideration of other domains of benefit of interest and value to patients
    o Adherence, convenience, monitoring, preferences

• Improved communication between all stakeholders
Benefit-Risk Considerations in Full Clinical Development: Challenges

• Multiple types of data
  ✓ Common metrics, data transformations

• Limitations of the RCT
  ✓ Clinical development population may not be as representative as actual use population
  ✓ Compliance/adherence

• Uncertainty

• Outcome prioritization
Benefit-Risk Considerations in Full Clinical Development: Value

• Enriched decision-making
  ✓ Structured, transparent process promotes quality decision-making informed by expert judgment
  ✓ Tools and processes for selecting, organizing, interacting with, and summarizing data relevant to benefit-risk decisions

• Communication and contextualization of benefit-risk
  ✓ Shared language and common understanding
  ✓ Displaying and communicating benefit-risk summaries
Visual Presentations of Benefit-Risk: Forest Plots with Endpoint Prioritization

Source: A presentation at the Society for Clinical Trials/Food and Drug Administration (SCT/FDA) benefit-risk workshop December 2013. “Benefit-Risk Assessment Methods: A Spectrum From Qualitative to Quantitative”
Benefit-risk assessment is a qualitative exercise grounded in quantitative data and expert clinical judgment, best supported by a structured approach.

Now...the task at hand is to adopt and integrate the use of framework-based benefit-risk assessment into our respective processes and deliverables.
Benefit-risk Assessment for Medicines on the Market

FasterCures Benefit-Risk Boot Camp
September 23, 2014

Frank W. Rockhold, PhD
Senior Vice President
Global Clinical Safety and Pharmacovigilance, GSK
What do we mean by Benefit and Risk?

- **Benefit**: what we want a treatment to do for patients and what is important about the outcomes
  - Clinically relevant outcomes or biomarkers / surrogates that are considered favorable effects and rationale for choosing them
  - Intensity, duration, and uncertainty of effects

- **Risk (Harm)**: the potential consequence to the patient and how to manage the events when they occur
  - Clinically relevant outcomes or biomarkers / surrogates that are considered unfavorable effects
  - Severity, duration, predictability, “monitorability,” and reversibility of effects

- **Benefit-Risk Balance**: how the favorable effects compare to the unfavorable effects

- “Asymmetry of Benefit: Risk Evaluation“*

*O’Neill, Drug Information Journal 2008 42: 235*
Gathering data in clinical trials from what they hope is a representative sample…

...as well as interviewing patients, e.g., in focus groups…

...and projecting back on the likely impact the medicine will have on a broader group of patients
Regulators are working at this level

Looking at information on multiple drugs, including clinical trial results, spontaneous reports, and sometimes observational data to understand how new interventions may affect morbidity, mortality, incidence, prevalence…

…as well as gathering information at patient meetings and through advisory groups.
A patient deciding on a treatment for themselves has to figure out where s/he is likely to fit

Will this help me or hurt me? Which one am I?
Patient health and public health

- Population v. individual benefit (prophylaxis)
- When is vaccination a choice and when is it a necessity? (school vaccinations, Ebola epidemic)
- Good for one or good for all? (risks and burdens for the larger populace when patients are more at risk and need more health care that they don’t want)
- How do I know that a prophylactic worked? Do I need to know? (screening, preventive medicines)
Changing perceptions of BR over the life of the medicine

<table>
<thead>
<tr>
<th>Stage</th>
<th>Question</th>
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<th>Question</th>
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</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>What will the drug do for the patient?</td>
<td>Do we need to design outcomes studies and what should they be?</td>
<td>What should be in the benefit/risk section of the dossier?</td>
<td>What should be emphasized in the risk(-benefit) communications?</td>
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<tr>
<td>Clinical study design</td>
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<td>Regulatory submissions</td>
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<tr>
<td>Launch</td>
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<td>Post-marketing surveillance</td>
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Perceived Benefit

BR proposition is at its maximum at Candidate Selection; perception of maximum benefit and low risk

Perceived Risk

Over time, less benefit observed or measured incompletely, e.g., surrogates, while accumulating more data on risks
<table>
<thead>
<tr>
<th>Benefit Harm Decisions</th>
<th>What part does patient input play?</th>
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</thead>
<tbody>
<tr>
<td><strong>Early development</strong></td>
<td>Where is the unmet medical need?</td>
</tr>
<tr>
<td><strong>Clinical development</strong></td>
<td>Is this clinical trial patient friendly? Are we measuring the right endpoints in the right way? Do we understand the course of the disease and its impact on the patient?</td>
</tr>
<tr>
<td><strong>Launch</strong></td>
<td>Will this be a medicine that patients want to take? Will it meet their priorities for their health? Have we provided enough information in the right way for patients to make informed decisions?</td>
</tr>
<tr>
<td><strong>Lifecycle</strong></td>
<td>What happens when patients are in an everyday clinical setting rather than a clinical trial? Where do patients go for information? How can we provide the information that is needed and trusted? How can we monitor patients’ wellbeing and medicine performance?</td>
</tr>
</tbody>
</table>

**Caveats**
- We can choose targets, but we can’t control what works
- Greater potency may mean greater toxicity
- Animal and in vitro models aren’t always predictive
- We should continue to look for more ways to involve patients at the disease level

**Caveats**
- We collect information from clinical trial patients and health outcomes studies, and extrapolate
- We are looking for the right population or subgroup and the right dose and regimen

**Caveats**
- We communicate some information in specific ways
- We need to be more creative and collaborative in the other ways we share information

**Caveats**
- The diversity of the environment requires a variety of methods
- **Collaboration is key**
Holistic Approach by the Medicine Safety Review Teams: Data from Many sources

- Drug class information
- Observational data
- Toxicology findings
- Product Complaints
- Laboratory Data
- Spontaneous Events
- Literature Reviews
- Social Listening
- Safety Summaries
- Serious AE’s
- Expert Opinions
- Regulatory Information
- Clinical Study Report
Benefit and Risk evaluated and reported on a regular basis:

PBRERs: Periodic benefit-risk evaluation reports

Integrated benefit-risk evaluation

– Relevant new safety information in the context of efficacy/effectiveness
– Cumulative from first marketing approval or first authorization for the conduct of an interventional clinical trial, but focused on new information,
– Includes relevant information from post-marketing studies or clinical trials in unapproved indications or populations
– Where relevant and appropriate, includes evaluation of safety data associated with uses other than the approved indication(s), reflected in the risk evaluation

Safety reported throughout clinical development

DSURs: Development safety update reports

- Annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed
  - examines whether in accord with previous knowledge of the investigational drug’s safety
  - describes new safety issues that could have an impact on the protection of clinical trial subjects
  - summarizes current understanding and management of identified and potential risks
  - provides an update on the status of the clinical investigation/development program and study results
- Assures that sponsors are adequately monitoring and evaluating the evolving safety profile of the investigational drug
- Includes relevant information from post-marketing studies
### Benefit Harm information beyond efficacy and safety

**How is it collected?**

<table>
<thead>
<tr>
<th>CONCEPT ELICITATION</th>
<th>PATIENT PREFERENCE-UTILITIES</th>
</tr>
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<tbody>
<tr>
<td>• Disease and treatment impact</td>
<td></td>
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<tr>
<td>• Definition of treatment benefit</td>
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</tr>
<tr>
<td>• Benefit-risk tradeoffs</td>
<td></td>
</tr>
<tr>
<td>• Complementary to clinical and safety data on benefits and risks of new treatments</td>
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<tr>
<td>• Used in economic evaluation to inform resource allocation decisions</td>
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<thead>
<tr>
<th>EXIT INTERVIEWS</th>
<th>CONJOINT ANALYSIS</th>
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<tbody>
<tr>
<td>• Explore indications</td>
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<td>• Understand benefits vs. risks</td>
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<tr>
<td>• Substantiate or complement other PRO measures</td>
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<tr>
<td>• Highlight potential issues for adherence to treatment</td>
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<tr>
<td>• Identify subpopulations with greatest response or patients unlikely to benefit from the treatment</td>
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<tr>
<td>• Used to understand patient preferences</td>
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</tr>
<tr>
<td>• Benefit-risk tradeoffs</td>
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<tr>
<td>• Inform drug development decision-making</td>
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Exit Interviews

Example of use

- Interviews conducted at the conclusion of subjects’ participation in a blinded clinical trial
- Can be used to:
  - Explore subjects’ experience with a drug
  - Understand benefits vs. risks (expected or not)
  - Substantiate or complement other PRO measures used in the study
  - Highlight potential issues for adherence to treatment
  - Inform clinical development plans
- Example: Drug X in development. Most competing drugs on market have a bothersome side effect A that often causes discontinuation. Drug X has a different, unique side effect, B. Use Exit Interviews to explore:
  - Experience of side effects
  - Sub-populations that could be willing or less likely to experience side effect B
  - Potential place in therapy for drug X
Clinical Development and Lifecycle

Patient involvement

- Post-clinical-trial questionnaire in oncology to incorporate their feedback in future studies
- Preference for delivery mechanism - mist v. eye drops for macular degeneration
- Disease severity (e.g., mild/severe IBS) to inform team and test hypotheses
- Advocacy groups describing the patient journey for families affected by immunodeficiency
- Expert patient protocol review of Phase II study of prophylactic approach to prevent or reduce diarrhoea
- Review of patient education materials for advanced kidney cancer and sarcoma by two expert patient groups
- Expert patient advocate review of Phase II trial to investigate management of pyrexia
- Disease severity (e.g., mild/severe IBS) to inform team and test hypotheses
Re-examining our approach

Needs of the patient should drive the development and lifecycle of a medicine

- Stages of disease rather than stages of drug development
- A whole person with symptoms we don’t think to ask about
- Trade-off disease v. treatment as competing risks
- Ultimate patient input is self-diagnosing and treatment
- Patients’ concerns with daily living
- Treating complications of one drug with more drugs
- Consideration of co-morbidities in selection of treatments

Ultimate patient input is self-diagnosing and treatment
There are many ways to collaborate

- Benefit – Risk is pre-competitive (and post-competitive), especially with the advent of regulatory changes and global interest

The landscape is changing

- Patient-led Benefit-Risk: member assessments, guidance documents, workshops
- ICH E2C Draft Guidance on PBRER includes effects on symptoms, quality or quantity of life
- FDA PDUFA V: BR Assessment and Patient Focused Drug Development
- PCORI: help patients and others make informed health care decisions
- FDA Patient Network
Thank you
Questions?