Today’s Webinar Audience
Polling Questions

- A small number of polling questions have been added to today’s webinar to make the session more interactive.
Contents

Evolution of Evidentiary Needs

The Right Question?

The Right Approach?

Future Trends?
Evolution of Evidentiary Needs

Does it Work?
Can it Work?
Is it Worth it?

Stakeholder Need

Global Healthcare Trends

- Divergent Economic Conditions
- Challenging Biopharma Environment
- Promise of Technological (r)evolution
- Strained Healthcare Environment
- Socio-demographic Shifts
- Rise of New Markets & Geographies
Evolution of Evidentiary Needs

Research Approach

- Genomics
- Patient Reported Outcomes
- Observational Research
- Pragmatic Trials
- Randomized Controlled Trials
- Case Reports

Evidentiary Needs

- Convenience, Quality of Life
- Safety, Effectiveness & Value
- Quality, Safety, Efficacy

Stakeholder Expansion

- Physician
- Regulator
- Payer
- Patient

1900 → 2020
The Right Question

Research Question

- value
- effectiveness
- quality
- safety
- efficacy
## Research Question Varies with Perspective

<table>
<thead>
<tr>
<th>Decisions Relevant to Medical Therapies</th>
<th>Example: Therapy for Osteoporosis</th>
<th>Research Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Approval</td>
<td>Is slow release sodium fluoride safe and effective for preventing fractures?</td>
<td>Safety, Quality Efficacy</td>
</tr>
<tr>
<td>Drug Coverage</td>
<td>Which bisphosphonate drugs should be included on a drug formulary?</td>
<td>Effectiveness</td>
</tr>
<tr>
<td>Clinical Practice Guidelines</td>
<td>When should therapy for low bone density be initiated?</td>
<td>Effectiveness Quality of Life</td>
</tr>
<tr>
<td>Patient Decisions</td>
<td>Should I take raloxifene, alendronate, or calcium and vitamin D to prevent osteoporosis?</td>
<td>Quality of Life Convenience</td>
</tr>
<tr>
<td>Health Plans and Insurers</td>
<td>Should we pay for follow-up assessment of bone density in women on treatment, and how often?</td>
<td>Effectiveness</td>
</tr>
<tr>
<td>Health System Policies</td>
<td>Should we institute primary care-based ultrasound screening for osteoporosis?</td>
<td>Effectiveness</td>
</tr>
<tr>
<td>Quality Measurement</td>
<td>What is an appropriate measure of high quality care in the treatment of osteoporosis?</td>
<td>Effectiveness Value</td>
</tr>
</tbody>
</table>

Atkins, D. Creating and Synthesising Evidence with Decision Makers in Mind. Medical Care 2007;45: S16-S22
Real-world Research

- Real-World Research is evaluation of effectiveness, safety and quality of care in settings and populations that are representative of practice including those not generally captured in traditional clinical trials. It can be characterized by:
  - Type of Outcome e.g. Clinical, Economic, Patient Reported
  - Research Approach e.g. Observational Studies, Pragmatic Trials, Database Studies
Demonstrating real-world value

*Payers opinions differ*

France and Netherlands are proactive in encouraging the development of real world evidence and in separate cases provide conditional reimbursement until the supportive real-world evidence becomes available.

Real world data are advantage but not an absolute requirement in the UK. NICE advises that registry data can be useful for utility data mapping, defining baseline data for patient subgroups, etc. However if data from registries/observation studies are supplied to show that effects from clinical trials can be replicated in the real world – is not required.

Though not fully embraced, payers are slowly beginning to turn to observational data to help understand a particular therapy. Registry data is not currently used to determine coverage or reimbursement decisions. There is an emerging interest and slow trend amongst payers in utilizing observational data for coverage decisions. As more real-world data becomes available, payers tend to consume more and demand more.

IQWIG refers to the discussion on pragmatic trials and views RCTs as feasible means to generate real-world data, depending on the appropriate trial design. Hence, with regard to the benefit assessment as a precursor for the cost-benefit-assessment, IQWiG is confined to RCTs if available but flexible with regard to the proximity of the trial design to routine care conditions. Real-world data generated by study designs other than the RCT are only taken into account by the institute if there is no alternative.
Regulators are Asking for More Nuanced Information

- FDA Sentinel Initiative
  - Expand access to sub-groups
  - Expand access to long term data
  - Expand access to adverse events occurring commonly in the general population

- EU Pharmacovigilance Legislation 2012
  Market Authorizations may be granted subject to conditions including:
  - Measures for the safe use to be included in the risk management system.
  - Post-authorisation safety and/or efficacy studies
  - An adequate pharmacovigilance system (routine condition) – pre-authorisation inspection provision
The Right Approach

Practical Considerations

- Budget?
- Time?
- Stakeholders & Needs?
- Research Question?
- Location?
- Data Availability?
- Research Availability?
- Language Considerations?
- Patient Availability?
- Site Availability?
- Standard of Care?
- Validated Instruments?
Ethical Considerations

- Conflict of Interest
- Patient Rights, Data Privacy
- Patient Safety
- Patient Population
Scientific Considerations

- Strength of evidence
- Research validity
- Choice of comparator
- Choice of outcome measurement
- Patient Segmentation
- Sample Size
- Duration of patient follow-up
## Strength of Evidence

<table>
<thead>
<tr>
<th>Observational Studies</th>
<th>Quality of Evidence</th>
<th>Randomized Controlled Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very strong evidence of association</td>
<td>High</td>
<td>Well-designed trials</td>
</tr>
<tr>
<td>Strong consistent association with no plausible confounders</td>
<td>Moderate</td>
<td>Study flaws</td>
</tr>
<tr>
<td>Dose response</td>
<td>Low</td>
<td>Indirect</td>
</tr>
<tr>
<td>Well designed studies</td>
<td></td>
<td>Sparse data</td>
</tr>
<tr>
<td>Few or inconsistent studies</td>
<td>Very Low</td>
<td>Very serious limitations to study quality</td>
</tr>
</tbody>
</table>

[www.gradeworkinggroup.org](http://www.gradeworkinggroup.org)
Research Validity

“Whether what is being measured is what was intended to be measured”

Internal validity
– The extent to which the findings of the study accurately represent the causal relationship between an intervention and an outcome in the particular circumstances of an investigation.

External validity
– The extent to which the findings obtained from an investigation conducted under certain circumstances can be generalised to other circumstances.

Choice of Comparator

AMNOG:
• Stringent selection of the cheapest appropriate comparator is set to represent a significant hurdle for Pharma market access
• Deviating from the G-BA’s selected comparator, without sufficient justification, will result in a negative pricing prospect.

“For us it is most important that we have valid head-to-head studies employing the right comparator drug. Based on clear evidence we want to see what value the new drug generates compared to existing treatments.”

Dr. Cornelius Erbe, President of the largest German statutory health insurance

Quintiles Confidential
Choice of Outcome Measurement

– Surrogate/intermediate or hard clinical outcomes?
– Individual or composite outcomes?
– Patient centred or disease focused?
HTA in diabetes: Patient Segmentation
Contain access to specific patient population

Clearly defined patient population with the evidence available for this particular patient group was necessary to obtain positive HTA opinion

CADTH recommended that restricting patient access to sitagliptin was essential for providing a positive reimbursement recommendation
- June 2008

SMC has approved Metformin powder for oral solution (Glucophage®) with the premium price for the treatment of type 2 diabetes mellitus, particularly in overweight patients. However restricted the use to patients who are unable to swallow the solid dosage formulation.
- April 2010

CVZ accepted exenatide for reimbursement only after restricting access to a subgroup of obese type 2 diabetes mellitus patients.

Original submission, September 2007

Clinical: No additional therapeutic benefit when compared to insulin for diabetes 2 patient population.

Economic: The cost effectiveness of exenatide was not sufficiently demonstrated for the whole population of type 2 diabetes patients (€17,979).

1st re-submission, January 2009

Clinical: Exenatide has shown added therapeutic value when compared to insulin therapy in very obese (BMI>35 kg/m²) patients with diabetes mellitus type 2.

Economic: The cost-effectiveness of exenatide versus insulin NHP is sufficiently demonstrated for type 2 diabetes patients with a BMI>35kg/m² (with an ICER OF €5,231).

Rejected. The addition of exenatide in therapy did not demonstrate any clinical or cost-effectiveness benefit for the patient population applied for.

Recommended for reimbursement only after restricting access to a subgroup of obese type 2 diabetes mellitus patients.

SMC: step-by-step approach for Exenatide

- in combination with metformin and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. It is restricted to use as an alternative to insulin in patients who have failed treatment on metformin and/or sulphonylureas and in whom insulin would be the next treatment option.
  - June 2007

“in combination with thiazolidinediones with or without metformin in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies. It is however restricted to use in combination with metformin and a thiazolidinedione as a third-line pre-insulin treatment option.”
  - March 2011

June 2007

Rejected.
The addition of exenatide in therapy did not demonstrate any clinical or cost-effectiveness benefit for the patient population applied for.

Quintiles Confidential
Sample Size and Duration of Follow-up

- It is a well-known fact that many biopharmaceutical products come to market with data on a few thousand patients.
- Large sample sizes are able to show small but significant treatment effects that are not demonstrated with smaller patient populations.

<table>
<thead>
<tr>
<th>Frequency of AEs</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>1000</td>
</tr>
<tr>
<td>0.1%</td>
<td>10,000</td>
</tr>
<tr>
<td>0.01%</td>
<td>100,000</td>
</tr>
<tr>
<td>0.001%</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>

- Data collected on patients over time (i.e., longitudinally) provides insight into:
  - effectiveness of long-term treatment
  - changes in treatment practice over time, including the impact of new treatment interventions as well as off-label use.
The Right Approach for the Right Question

Interventional

Prospective Observational (including registries)

Retrospective analysis of existing clinical or administrative data
Focus on Intervventional Designs

Studies designed to test a hypothesis by modifying an exposure within the study population

Intervventional

Prospective Observational (including registries)

Retrospective analysis of existing clinical or administrative data
# Interventional

## Explanatory Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Features</th>
<th>“Gold standard”, randomized, blinded, placebo controlled to measure efficacy in highly selected patients with standardized and intense follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>The only known way to avoid selection bias and confounding. Especially useful for examination of small or moderate effects.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Can be low on external validity making results difficult to generalize to the target population. In some situations it is not ethical to randomize patients e.g when there is a known safety risk. Costly.</td>
</tr>
</tbody>
</table>
## Interventional

### Pragmatic Randomized Trials

<table>
<thead>
<tr>
<th>Features</th>
<th>Randomized, open-label, with ‘usual care’ control group to measure effectiveness in broad patient population with follow up.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Balance internal and external validity to provide a more representative estimate of benefit/harm in typical patients. Patient enrolment is not dependent upon prescribed treatment adoption. PCTs can be used to test hypotheses.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Real-world setting introduces variability. Compared to a RCT the effect size may be diluted. Physicians are typically not routinely involved in research and need support. Quite costly.</td>
</tr>
</tbody>
</table>
Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)

- Practitioner expertise (experimental)
- Flexibility of experimental intervention
- Eligibility criteria
- Primary analysis
- Practitioner adherence
- Outcomes
- Participant compliance
- Follow-up intensity
- Practitioner expertise (comparison)
- Flexibility of the comparison intervention

Thorpe et al 2009
CMAJ:180(10)
Focus on Prospective Observational Designs

Describe patterns of health and disease without doing anything to change factors that influence them.
Observational

<table>
<thead>
<tr>
<th><strong>Features</strong></th>
<th>Non-randomized non-interventional studies that monitors a cohort(s) over time. Patient registries may focus on disease, product or exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Examine longer-term outcomes in populations typically excluded from trials and examine risks for uncommon harms and factors that modify risk. Produce more representative data on a range of outcomes, including harms, and can be more cost-effective than randomised trial designs. They also allow assessment of actual use (including off-label) to identify potential new indications. Can be particularly useful for studying rare exposures and more than one outcome.</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>These studies are prone to bias and confounding. Only the most well designed and consistent studies are considered to provide moderate to strong evidence making optimal design, conduct and analysis critical.</td>
</tr>
</tbody>
</table>
Focus on Retrospective Designs Using Routine Data

Studies that mine routine data repositories for information, including paper and electronic health records and administrative databases

- Interventional
- Prospective Observational (including registries)
- Retrospective analysis of existing clinical or administrative data
Retrospective Designs Using Routine Data

<table>
<thead>
<tr>
<th>Features</th>
<th>Database epidemiological studies use routine data repositories, including paper and electronic health records and administrative databases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Database Epidemiological Studies can be used to assess benefits and harms across an extremely large population and are cost and time efficient compared to prospective, longitudinal research.</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>The underlying information is not collected in a systematic way and it is difficult to interpret missing data. Data abstraction from paper records is resource intensive and, complete medical and clinical histories may not be available (e.g. where a patient was referred to the clinic) and administrative databases and electronic health records are not uniformly available across all countries. Privacy issues may also create the need to aggregate data.</td>
</tr>
</tbody>
</table>
A Plethora of Methodological Standards & Good Practices Underpin Best Practice Research Approaches

<table>
<thead>
<tr>
<th>BODIES OF EVIDENCE</th>
<th>Systematic Reviews &amp; Meta-analyses</th>
<th>PRISMA, MOOSE, Cochrane Reviews, AHRQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grading Systems and Tools for Studies</td>
<td>GRADE, AMSTAR, AGREE, COGS</td>
</tr>
<tr>
<td>INDIVIDUAL STUDY TYPES</td>
<td>Randomized Clinical Trials</td>
<td>CONSORT, CONSORT – pragmatic trials, PRECIS</td>
</tr>
<tr>
<td></td>
<td>Observational</td>
<td>GRACE, STROBE, ISPOR, AHRQ</td>
</tr>
<tr>
<td></td>
<td>Other Applications</td>
<td>Sox et al., STARD, STREGA, SQUIRE, REMARK, TREND, ENcEPP, GPP</td>
</tr>
</tbody>
</table>

Future Trends
Approaches will Converge

- Interventional
- Retrospective analysis of existing clinical or administrative data
- Prospective Observational (including registries)
Hybrid designs may capitalize on the speed, cost efficiency and strength of different methods

Utilizing retrospective and prospective data to shorten time and cost

Conducting sub-studies alongside larger simple prospective research endeavours

- Health Economic Study
- Large Pragmatic Trial
- Or
- PRO Study
- Disease Registry
- Etc.
Support quicker and more economic recruitment and follow-up of RCTs...

Improve patient safety...

Support large scale phenotype-genotype association studies and follow-up on trials...

Drive the integration and re-use of clinical data stored in different eHR systems...

Enhance uptake of eHR systems that offer support for clinical care and research...

...with an integrated eHR interface that enables the rich capture of clinical data, including symptoms and signs

...by providing not only a diagnosis support tool but also a functional eCRF that supports the identification of patient eligible to participate in clinical trials

... through distributed interoperability of eHR data and clinical data repositories that maintain provenance, confidentiality and security

... with software tools and web-services that support clinical research by enabling use of controlled vocabulary and standardised data elements

... by adopting an open-source business model, allowing eHR vendors and data integrators direct cost savings and the ability to reach more customers through improved pricing flexibility
PRESS RELEASE

STRICTLY EMBARGOED UNTIL 10.15AM FRIDAY 2 MARCH 2012

Issued: 2 March 2012, Salford and London, UK

Innovative UK research project to study the value medicines bring to patients in the real world

Unique collaboration to ensure medicines under development meet patient and healthcare system needs

A new way to study the value medicines bring to patients and healthcare providers has launched in the north west of England. The innovative ‘real-world’ research project will study the safety and effectiveness of a GlaxoSmithKline (GSK) late-stage investigational respiratory medicine alongside currently available treatments, as thousands of patients manage their chronic obstructive pulmonary...
Access to patient communities offer a new channel for observational research

**Observational Research**

- **Retrospective** (EMR, Claims)
  - Unstructured (e.g., scanning blogs for adverse events)
  - Structured (e.g., TSQM data)
- **Prospective** (Site-based enrollment)
  - Cross-sectional (e.g., burden of illness, disease prevalence)
  - Longitudinal (e.g., registries)

**Direct to Patient Research**
Conclusion

- Stakeholder Need
- Research Question
- Research Approach
- Insight
Upcoming Events

– Webinar
– April 17, 11am EDT
– Registration link: https://www1.gotomeeting.com/register/701354816

Thank you

louise.parmenter@quintiles.com