Listening to children’s and parents’ voices: Using Patient Reported Outcomes to empower patients with orphan diseases and their parents

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Agenda

• What are the barriers to paediatric clinical trial research in rare diseases?
• How can children’s/parents’ voices be heard in clinical trial research?
• How should paediatric PROs and ObsROs be developed?
• How can they be used to maximize voices being heard?
Traditional Barriers to Paediatric Rare Disease Research

- Assumption that children are healthy
- Staging of disease difficult
  - ‘Early’ stages hard to determine
  - Assessment of deceleration of development, not just deterioration
- Ethics
- Growth & development rapidly changing
- Market perceived as relatively small – not worth the investment?
How can children’s and parents’ voices be heard in clinical trial research?
COAs provide key information for assessing treatment benefit

**Clinical Outcome Assessments (COAs)**

- **Biological**
  - Measurement based on objective clinical outcomes of therapy.
  - Includes direct measure of disease activity (e.g., tumor size), biomarkers (e.g., PSA) & pure outcomes (e.g., survival).

- **Patient Reported Outcomes (PROs)**
  - Measurement based on self-report by the patient about their condition and treatment.
  - Examples: symptoms, HRQoL, functional status, treatment satisfaction, adherence.

- **Clinician Reported Outcomes (ClinROs)**
  - Measurement by observer with relevant professional training (e.g., clinician).
  - Of value in cases where patient is unable to provide a reliable self-report, e.g., neurological or psychiatric conditions. Opioid addiction project.

- **Observer Reported Outcomes (ObsROs)**
  - Measurement by non-clinician observer e.g. teacher or caregiver.
  - Of value when patient is unable to self-report (e.g., infants, young children).
  - Should only be based on observable concepts (e.g., signs or behaviors).
Examples of Child Items

Last night in bed, how much did your cough keep you awake?

- Not at all
- A tiny bit
- A little
- Some
- A lot

The last time you pooped today, how hard did you push?

- I didn’t push hard at all
- I pushed a little hard
- I pushed very hard
- I don’t know

Did you feel gassy today?

- A tiny bit
- A little
- Some
- A lot
Avant de commencer à remplir le questionnaire, merci d’inscrire la date d’aujourd’hui :

Jour  Mois  Année

1. Est-tu inquiet par l’hémophilie ?

- Je ne suis pas inquiet
- Je suis un peu inquiet
- Je suis très inquiet

2. As-tu peur des piqûres ?

- Je n’ai pas peur
- Je n’ai pas peur
- Je suis très peur

3. Est-ce que les piqûres te font mal ?

- Elles ne me font pas mal
- Elles me font un peu mal
- Elles me font très mal
How should PROs/ObsROs be developed?
What makes a good PRO/ObsRO?

Standards for the Development and Validation of PROs are detailed by US & EU Regulatory authorities:

- FDA PRO Guidance, 2009
- EMA Reflection Paper, 2005
BUT....Minimal Statements on Paediatrics; none for Orphan indications

“It is important that PRO instruments developed for adults are not used in pediatric populations unless the measurement properties are similar in all groups tested.”

“Additional review issues include age related vocabulary, language comprehension, comprehension of the health concept measured and duration of recall”

• Instrument development and validation testing within fairly narrow age groupings is important...to determine the lower age limit at which children can understand the questions and provide valid and reliable responses
How do you develop a paediatric PRO/ObsRO?

- Literature review
- Open-ended interviews w/population of interest or focus groups
- Interviews w/clinicians
- Saturation of concepts

Establish important measurement concepts: Talk to patients/parents across age ranges

- Cognitive debriefing interviews
- Items/concepts clear and relevant
- Recall period acceptability
- Response scale well defined
- Format/instructions
- Translatability
- Expert input

Ensure respondent understanding: Talk to patients/parents across age ranges

- Reliability (internal consistency & test re-test)
- Concurrent /convergent validity
- Discriminant validity
- Responsiveness
- Definition of clinically meaningful outcomes
- Expert input

Ensure measure performs as intended: test with patients/parents across age ranges

Strong qualitative research with population of interest is key: “The most critical consideration is whether content validity has been established with input from respondents in the target population” – Laurie Burke
Challenges specific to paediatrics and orphan diseases

- Paediatric/orphan literature is often very limited, particularly qualitative literature
- Despite the need to evaluate the outcomes in narrow age ranges, studies often have very broad age ranges

Solutions

- Consider the grey literature
- Prospective qualitative research and input from expert clinicians assume greater importance
Interviewing for Concept Elicitation and Content Validity Testing

**Challenges specific to paediatrics and orphan diseases**

- Limitations in memory, cognitive ability, language comprehension by age
- Children can be shy and lack vocabulary
- Rarity of condition may make recruitment/saturation difficult to achieve
- Parents are unable to report on some symptoms/domains not known to them

**Solutions**

- Carefully guided interview guides and well trained interviewers
- Creative interview techniques, toys and drawings
- Collapse age groups where appropriate
- Must achieve saturation within each narrow age range – can this be relaxed for orphan indications? Get FDA buy-in early
- Consider other respondents (teachers? Nanny?)
What can you ask in an interview?

Type of questions need to vary by age group and respondent (disease and cognitive/motor/emotional development dependent)

0-2: Parent as proxy
- Focus on observable behaviours

3-5: Parent as proxy
- Observable behaviours plus more activity oriented questions

6-8: Child and parent
- Can ask simple, direct, concrete questions of child
- Avoid recall periods, drawings and toys can be helpful

9-11: Child and parent – pre-pubescent
- Drawings and toys helpful; still use simple child-friendly wording

12-17: Adolescents
- Can use more adult language, but no jargon; can be more complex
Interviewing Tools

Creative activities, such as using Play-doh® …...

When it’s like that, it’s sometimes harder to come out (male age 17)

I’ll say it feels long. And it feels - it make me feel different...wait, not different. It feels better. I feel better after I went. (male, aged 7)

“I drew me, like me on the toilet. And I feel sometimes I might cry. And like my stomach, it feels like it’s almost like howling, it’s going” RRRR. (female, age 12)

….and drawing their symptom experiences helped children to describe and discuss their symptoms and related impacts.
Development/Selection of PRO/ObsRO

Next step is to either:

a) Identify a PRO that has questions that measure all key concepts (using appropriate wording)

OR

b) Develop a new PRO questionnaire or adapt existing questionnaire
   • PRO questions must be clear, simply worded (using child words identified from qualitative research)
   • Short recall periods
   • Simple responses options recommended
   • Can consider using response with faces or circles
Selecting Existing PRO/ObsRO Instruments for Trials

Challenges specific to paediatrics and orphan diseases

- Relatively few disease specific pediatric measures exist, even fewer in orphan diseases
- Who should you ask?
- Existing PROs/ObsROs often inadequate to support FDA label claims
- How should you ask?

Solutions

- Think about PRO selection early, allowing time for development/adaptation/validation, possibly using trial data
- Talk to patient advocacy groups
- Consider all types of respondents (parent/teacher/nurse/child)
- Engage FDA early
- Consider EPRO vs pen/paper vs IVRS
Caregiver Completed Measures

• Focus on “observable behaviours”
  o Strongly recommended by FDA
  o Things parent/caregivers can see, hear or feel (by touch)
  o e.g. “Did you see your child cry in the last 24 hours?”
    and/or “Did you see your child holding his/her stomach like it was hurting in the last 24 hours?”

NOT
  “Did your child have abdominal pain in the last 24 hours?”

• But what about sensations that are not observable but the child can report to the parent?
  o Is it ok to ask about what the child told the parent?

• Can the parent/caregiver report if he/she has not spent the whole day with the child?
Measures of Caregiver/Family Impact

- Often overlooked

- Caregiver/family impact can be considerable and may be what can be most reliably measured

- Can include:
  - Work/productivity impact
  - Emotional impact
    - Anxiety/worry
    - Guilt
    - Depression
    - Frustration/anger
  - Social Impact
  - Sleep impact
  - Tiredness/fatigue
Content Validity Testing

Challenges specific to paediatrics and orphan indications

- Hypothetical situations don’t work with children
- Children try to give you the answers they think you want to hear and struggle to understand the questions
- Small sample sizes in rare conditions

Solutions

- Allow child to complete diaries at home for a few days prior
- Carefully guided interview guides and well trained interviewers
- Questioning should not be too repetitive nor lengthy
- When analysing, check for consistency for response and consistency between behaviour and responses
- Collapse age groups where appropriate
Psychometric Testing

Challenges specific to paediatrics and orphan indications

- Sample should be stratified by age group but small samples in orphan indications
  - Necessary to demonstrate validity/efficacy in each age group as well as overall sample
  - Increases the sample size required for validation

Solutions

- Consider validating as part of trial and/or include data from cognitive debriefing (move forward at risk)
- Consider collapsing across age groups, if possible
- Consult regulatory early
- Utilize psychometrics done in other diseases if adapting a measure
If so complex, why bother?
How can PROs/ObsROs be used to maximize voices being heard?
PRO/ObsROs inform healthcare decisions throughout the product lifecycle

Discovering
Clinical development
Commercialisation

Research
Development
Phase I
Phase II
Phase III
MAA
P&R
Launch

Quality
Safety
Efficacy

Market authorisation application

Pricing and reimbursement
“Fourth hurdle”

Affordability
“Fifth hurdle”

Product licence

Product access to market

Market access to product
COA Applications: Informing healthcare decisions

Clinical trials
- Regulatory drug approval
- Promotion/advertising
- Generation of evidence for communication

Real-world & phase IV studies
- Observational studies
- Identifying unmet need for new products
- Identifying application of existing products in new population
- Post-surveillance safety monitoring

Clinical practice
- Screening tools, e.g. suitability for treatment
- Improving clinician-patient communication
- Monitor treatment effectiveness in the clinic
- Monitor adherence and “individualized medicine”
COAs key to getting regulatory approval: Example of Icatibant for the treatment of Hereditary Angioedema

“It was every probably every other week I was rolling around on the floor being violently sick and in excruciating pain.”

“You can have a severe swelling in the hands as well but - which depends on the size of the swelling.”

“Well, when it is in my throat, er... and you can neither swallow nor speak right.”

“I used to have weekly attack where I've been sick, blacking out, couldn't move, couldn't do anything. Couldn't possibly get out of bed for my injection.”

Clinical trials using PROs as primary & secondary endpoints

2005 - 2009

2009

New trials revised PROs

2010

2011

Jerini receives European Commission approval for Firazyr (Icatibant) but FDA Issues Not Approvable

Winter 2011: European Commission Approves Self-

"I would vote yes, in capitals, and urge the agency and the sponsor to expedite the whole process and what they can do to get this approved, as well for self-injectable use," Recommends Approval and Self-Administration of FIRAZYR® (Icatibant) for the Treatment of Acute Attacks of Hereditary Angioedema
Informing Decisions on Product Value (Pricing/Reimbursement): Iron Overload (Exjade) for B-thalassaemia and sickle cell disease

Significant HRQOL burden and low levels of tx satisfaction in patients receiving traditional treatment for iron overload via 8-12hr subcutaneous injection 5-7 times per week

HRQOL and treatment satisfaction data collected as part of clinical trials for Exjade (a once daily oral iron chelator) using generic (SF-36) and bespoke PROs (SICT)

Studies demonstrating improvements in HRQOL, treatment satisfaction and adherence in patients receiving Exjade and communicated via external publications before market access application
Informing Decisions on Product Value (Pricing/Reimbursement): Iron Overload (Exjade) for B-thalassaemia and sickle cell disease

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Studies demonstrating improvements in HRQOL, treatment satisfaction and adherence in patients receiving Exjade and communicated via external publications before market access application. Implicit use of reference to PRO research in decisions by UK and EU decision makers.

| FR          | • Reference to HRQL benefits, mode of administration  
|            | • Better management of patients (poor compliance with DFO) |
| NL         | • Oral therapy associated with improvement in HRQL  
|            | • Credibility of utilities acknowledged |
| UK         | • Utility: explicitly considered (driver of cost-effectiveness)  
|            | • Consistency: Utility ↔ HRQL  
|            | • HRQL/convenience/preference mentioned in guidance |
Take Home Messages

- What are your plans for paediatric PRO research?
- Paediatric research is more complex than adult research – consider age, developmental changes
- BUT it is possible with careful planning and a solid understanding of child development

And........

IT’S MUCH MORE FUN!