Patient reported outcomes and clinical and translational research

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Why consider patient-reported outcomes PROs at all in the translational research continuum?

- More obviously relevant in the 5- than the 2-stage continuum

- How does a PRO get developed & what does it address?

- What can a statistician do to address the challenges that PROs raise in clinical and translational work?
* FDA requires PROs in clinical research submissions.
* Advocacy groups (& PCORI) seek to have patients’ “lived experience” included in clinical research.
* PROs can be developed from/focused on the clinician perspective or the patient’s perspective.
  * Clinical perspective may be more relevant for translational work, but the patients’ perspectives is relevant for work on cost effectiveness and FDA approvals.
  * Patient perspective is often obtained as “quality of life”
The typical PRO is “quality of life”

- Patients’ “lived experience” with disease/disorder; the impact of signs/symptoms on their ADLs/life.
- “Quality of life (QoL) is the gratification taken from life, happiness, and the way human beings perceive their situation within the system of culture and values.” Garup et al. 2011.
- “Asthma-related quality of life” refers to the perceived impact that asthma has on the patient’s quality of life. (Wilson et al. 2012)
- Clearly impossible features of preclinical work. A challenge is, how to infuse the PRO earlier than T3-T5.
  - What if an intervention succeeds wildly at T1-T2, and has zero impact on patient QOL? Payors will not pay; FDA may not approve!
### Translational stages

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<th>T3</th>
<th>T4</th>
<th>T5</th>
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<tr>
<td>Basic science</td>
<td>Preclinical work</td>
<td>Clinical trials/clinical efficacy</td>
<td>Wider clinical practice/phase iv</td>
<td>Policy/public health, incl cost effectiveness</td>
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<tr>
<td>No possible relevance of patient’s lived experience</td>
<td>possible relevance of patient’s lived experience (safety, AEs)</td>
<td>dependence on patient’s lived experience (FDA applications)</td>
<td>Critical dependence on patient’s lived experience</td>
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Whether you subscribe to a 5- or fewer-stage model of translational work, the patient’s lived experience has a varying **relevance** - from none at all to critical!
Where could a PRO contribute?

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- QOL captures **impact** of symptoms <on humans> - virtually impossible to conceptualize/model T1(-T2).

Suddenly, QOL/PRO appears in T3 and must appear T4-T5.
The origins of the PRO matter

“Traditional” PRO developmental model:
* Accommodates research into biological bases of clinician perspective (e.g., symptoms) and NOT patient’s perspective.

NEW PC-PRO developmental model:
* Accommodates research into biological bases of patient’s perspective (and includes clinicians’).
Biological underpinnings of pt experiences

- Developing an instrument that is **PC-PRO** (Tractenberg et al. in press) about urinary symptoms for patients with neuropathic bladder (NB).
  - Patients with NB have spinal cord injury, spina bifida, or multiple sclerosis.
- Followed new PC-PRO development model, collecting urine samples from participants who use the new PC-PRO, and running genomic analyses to identify pathogenic contributions to specific signs and symptoms.
  - *Unlikely* these align for QOL- or impact-driven assessment.
- Because outcome is specifically PC-PRO, this metagenomic work can actually contribute to design and analyses T1-T4.
- Because the outcome is PC-PRO, biological results can contribute importantly to design and analysis T5.
General challenges in translational work

* Prinz et al (2011) note that the unreproducibility of results at T1 (basic) and into T2 (preclinical) undermines the potential for clinical trials (T3)
  * And, the lack of alignment of outcomes useful in T1/T2 to what will be needed in T3-T5 is also problematic.
  * (lack of alignment of outcomes across the translational continuum may be causal for these failures!)
* Jogalekar (2012) criticizes translational work because it requires that an application is identified before the research ideas (ie, basic scientific questions) are even answered.
  * Understanding the biological underpinnings of the patient’s lived experience, rather than the clinicians’ perception of symptoms, constitutes “basic scientific questions” that need to be answered (if you want FDA approval eventually).
When planning clinical trials/studies, statistician can advocate for PROs with a) some symptom specificity; and b) clear patient-centeredness;

* new publication opportunity (-ies) to document these properties.

When planning preclinical research, statistician can initiate analyses (or simulations) to test or formulate hypotheses about how patients -and/or their symptoms - may be impacted.

Combine qualitative and quantitative methods to understand how PRO items (not “total scores”) change.

Exploit nonparametric methods for appropriate estimation of change (e.g., Tractenberg et al. 2013).
Take home messages

* FDA requires PROs in clinical research submissions. Phase III and IV should feature PRO input.
* Roles for PROs in translational research (2-stage, 5-stage) abruptly change from “none” to “important”.
* PROs developed with the patient’s perspective on symptoms central (i.e., patient-centered or PC-PROs) CAN be linked back to earlier translational stages.
* When planning clinical trials/studies, statistician can advocate for PROs with a) some symptom specificity; and b) clear patient-centeredness; new publication opportunity (-ies) to document use/alignment of PC-PROs with earlier translational-stage work.
References


* Prinz, Florian. "Believe it or not: how much can we rely on published data on potential drug targets?". Nature Publishing Group. Downloaded 16 Jan 2017 from http://www.nature.com/nrd/journal/v10/n9/full/nrd3439-c1.html

