PRO endpoints
Academic perspective

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Shift in trial design

Old model

- Classic trial design
  - Fixed population
  - Fixed intervention
  - Fixed characteristics
- PRO instruments
  - General coverage
  - Paper administration
  - Static questions

New model

- Novel trial design
  - Basket trials
  - Umbrella trials
  - Adaptive designs
- PRO instruments
  - Tailored topics
  - ePRO
  - Dynamic question set

Increased flexibility but also uncertainty in validation, implementation and interpretation

PRO design of a clinical trial

PRO hypothesis

Evolution in control group
- disease + treatment
- pattern over time
- data available?

+

Treatment effect
- Domains of interest (what)
- Timing (when)
- Magnitude (how)

Multi-stakeholder

Tools to be used

Assessment schedule

Statistical test

Trial design
- **PRO often secondary endpoint**
- **Availability of tools**
- **Logistical constraints**

Goal = practice changing

Current state

“One hypothesis fits all” = outdated.

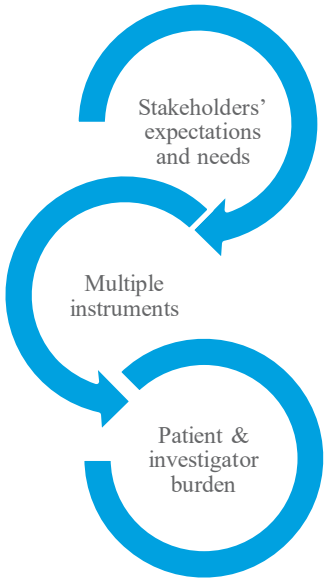
- Standard PRO chapter added to clinical trial: insufficient
  - “compare QoL profiles”
- Tailored approach: measure what matters
  - Value for patients, clinicians, regulators, HTA, …
  - Level of involvement varies.

Positive evolution

How to elicit expectations/needs?

More tailored = more complex

- Issues change faster than questionnaires
  - Treatments evolve → side effects evolve (e.g. rash)
  - PRO hypotheses get more specific and diverse
  - Clinical trials get more complex
- Updating or creating new questionnaires = inefficient
  - Time and resource consuming process
- Result: multiple questionnaires with broad issues
  - Patient burden: impact quality of data
  - Negative results: difficult to detect treatment differences



Increased Complexity: How to Respond?

- **PRO hypothesis: key component**
  - Must be relevant to research hypothesis (but not excessive)
    → not simply done because of "tradition"
- Careful selection and administration of instruments
  - Patients must see the tools as meaningful (increased motivation)
  - Minimizing overlap between measures

Difficult to achieve with static questionnaires.

- Shift to dynamic, patient-centered tools
  - Item libraries → more relevance
  - Computerized adaptive testing (CAT) → more precision

Item Libraries

Select questions specific to the research hypothesis.

- reduce burden by minimizing number of questions
  - Less redundant or irrelevant questions
- Increased flexibility and efficiency
  - More tailored to the needs of specific treatments and populations
- Feeds back into the questionnaire development cycle
  - If specific item combination is popular → standard questionnaire?

Allows to create ad-hoc item lists specific to a given trial

Computerized Adaptive Testing (CAT)

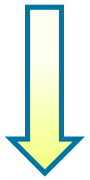
CAT = dynamic questionnaire set

- No fixed list of questions but an underlying 'pool' of questions
- **CAT selected question → Information gain is maximized based on previous response(s)**

- Can work in conjunction with item banks/libraries.
- Relies on item response theory (IRT)
  - Shorter and/or more individualized measures
  - Increased construct validity
  - Higher precision
- Can be used for scales of interest to **maximize precision**.
- Can be used where floor/ceiling effects are expected.

→ Result: more sensitive to specific treatment effects.

Static: multiple 'similar' questions at once
Dynamic: tailored questions in succession



Outcome for each patient
Not all patients answer the same questions

Not yet systematically used in clinical trials → understanding/acceptance by stakeholders

Trial design implications

Item Library + CAT allow

- Better trial **tailored** questionnaires → construct tailored hypotheses
- Reduce patient/investigator **burden**
- Preserve access to **historical** data / context

BUT:

- Construction/selection guidelines?
- Validation status – what checks are needed?
- Loss of standardization
- Logistics

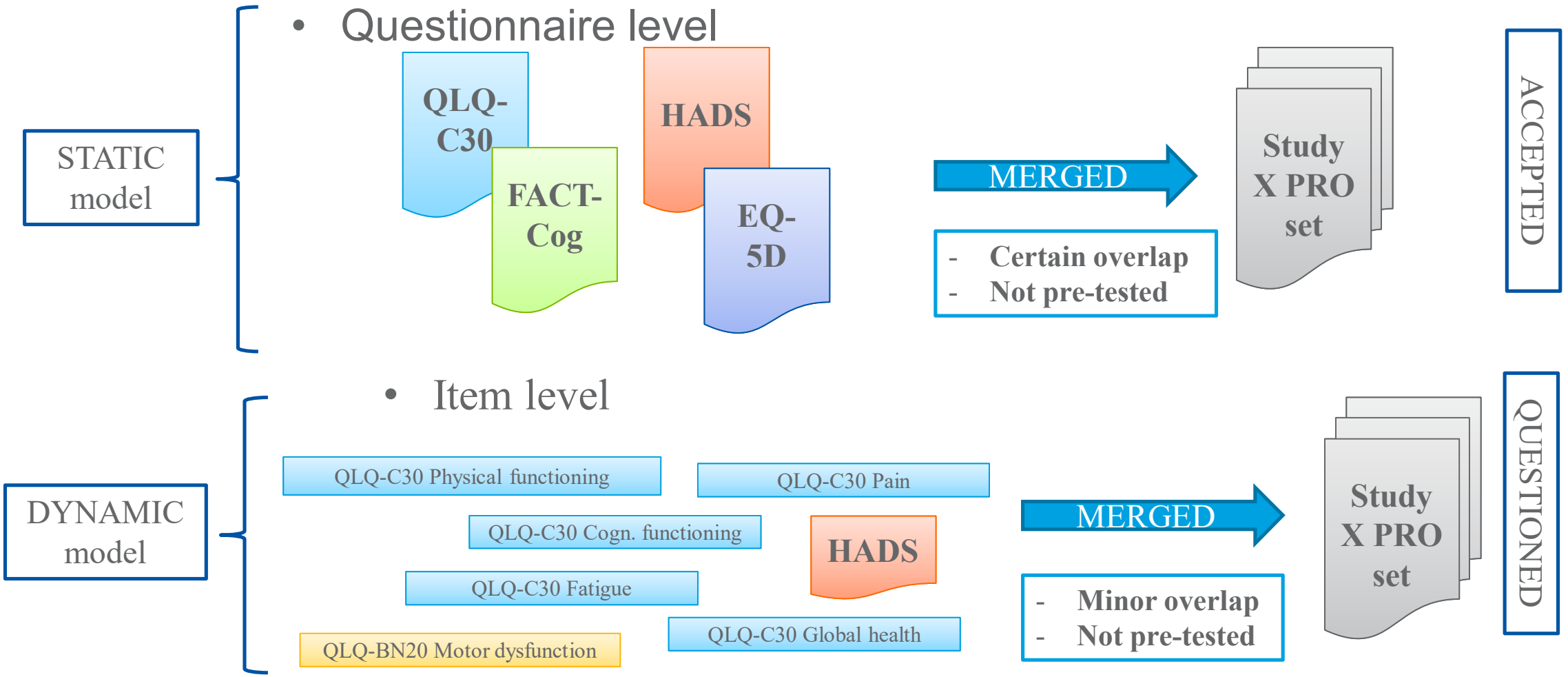
Validation of Library Item Lists

‘ITEM LIST’ to distinguish from questionnaire.

Validation?

- Reliability (Test-retest)
  - Test-retest reliability: OK.
- Sensitivity/responsiveness
  - discriminate between or within patients: OK.
- Content validity
  - Face validity
    - extent to which items reflect the intended domain of interest: OK
  - Criterion validity
    - compare against an ‘gold’ standard: OK
  - Construct validity:
    - questions correlate with their domain: depends on selection.

EORTC Item Library Item Lists



Trial logistics

- CAT requires ePRO
- Questionnaires constructed from item libraries can be ePRO or paper, if:
  - Items originate from paper instrument.
  - Conditional/adaptive items are minimized
    - E.g. different questions depending on gender, disease status, …

- Acceptance by review committees?
  ethical committees, regulatory agencies, patient reps, …?
  - Eg. require print version of all questions
  - N° of questions will vary

Flexibility (advantage) ↔ Uncertainty (disadvantage)

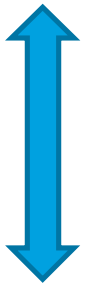
Loss of standardization

- Design:
  - Use of historical data? CAT precision level?
- Analysis:
  - Item list: according to source.
  - CAT: Patients with same score = different questions
  - MIDs (clinical threshold): transferrable?

- Reporting:
  - Report item list results? CAT reported as original scale?
  - Multi-stakeholder = different expectations (beyond trial)

→ Science advances using a cumulative body of evidence

Need to build better understanding and experience



Need for better standards in design, analysis and reporting

Future strategies

- **PRO guidelines needed for the new era**
  - Emphasis on tailored PRO hypothesis
  - Allow flexibility for multiple stakeholders
  - Maintain consistency

- Static questionnaires have advantage of **standardization**.
  - Core set of QoL issues (eg. Reeve et al, JNCI 2014)

- **Compromise between flexibility and standardization**:

  'Core +/- Extension +/- Item List Strategy' ***(Groenvold et al, CCR 2016)***

  - Core set allows cross-trial comparison (Anchoring + Utility)
  - Fixed extensions: ensure adequate coverage
  - Item List to cover missing trial specific issues

Conclusion

Tailored PRO design to become the norm.

- For successful patient-reported trial outcomes:
  - Increased attention to hypothesis
  - Make **flexible tools more accessible, acceptable and relevant**
  - Adequate analysis, publication and access to results

- Practice changing trials for all stakeholders:
  - Involve stakeholders in the design: directly or indirectly
  - Be aware of the available tools and methods: advantages + disadvantages
    - Static tools still have a role to play.
  - Analysis and reporting: different stakeholders = different needs
    - Access and understanding of the outcomes.

- **Maintain a level of standardization**: 'core + extension + itemlist'

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- EORTC Item library
https://www.eortc.be/itemlibrary/

- EORTC CAT
https://qol.eortc.org/cat/