Considerations for Assuring Quality Tools and a Proposal for Open Software Development Standards

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Bedside Pharmacometrics, aka...

- Precision Medicine
- Accuracy Medicine
- Personalized Medicine
Considerations for Quality Bedside PMX Tools

- Scientific Validity
- Algorithm Verification
- Software Development Process
- Interoperability and Accessibility
Considerations for **Quality Bedside PMX Tools**

- What is the scientific basis for pharmacometrics-guided decision making?
- Is there sufficient clinical evidence for the proposed intervention?
  - Prospective clinical trials
  - Retrospective review
  - Clinical habit
Scientific Validity of Clinical Intervention

- Infliximab TDM
- Week 10 IFX level
  - < 20 mcg/mL
  - 20 to < 25 mcg/mL
  - > 25 mcg/mL
- Retrospective cohort study
- Singe site

What is the basis for infliximab exposure target?

“Data on the benefits of proactive TDM on infliximab durability and immunogenicity in IBD are still limited.”
Considerations for **Quality Bedside PMX Tools**

- How will model-based methods inform clinical decision-making?
  - Estimation of model parameters
  - Projection of expected concentration or response time-course

- Has the algorithm performance been evaluated under realistic conditions?
Algorithm Verification: MAP Bayes Estimation

- Which way will the balance tip between prior knowledge and new data?
- Individual estimation is driven by relative magnitude of residual variability vs. inter-subject variability
Algorithm Verification: MAP Bayes Estimation

- Accurate new data point pulls estimate toward true individual prediction, but not entirely
- Population prior still has influence (so-called eta shrinkage)
Algorithm Verification: MAP Bayes Estimation

- Erroneous new data point pulls estimate toward severely biased individual prediction
- Population prior has little/no influence (so-called eps shrinkage)
Algorithm Verification: MAP Bayes Estimation

- Guidance via parameter estimation (e.g. CL) may be further complicated by lack of identifiability at individual level (too much estimation flexibility)
- Apparently accurate model predictions are not a guarantee of unbiased parameter estimates, or accurate individual estimation
- MAP Bayes typically lacks measure of estimation precision
- Consider iterative update of priors
- Evaluate performance prospectively through simulation studies before deploying bedside tool
Considerations for **Quality Bedside PMX Tools**

- Does software development follow professional and regulatory standards?
  - A formal software development life cycle process
  - Software validation with documentation
Software Development Life Cycle

Waterfall

Open SDLC - https://github.com/metrumresearchgroup/open-sdlc

https://www.digite.com/blog/waterfall-to-agile-with-kanban/
Considerations for Quality Bedside PMX Tools

- Is the framework for delivery of model-based clinical guidance interoperable with other clinical systems?
- Is the tool accessible to clinical decision makers across the health care delivery system?
Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.
Open Source Software Quality

- Professional and Regulatory Standards
  - Software Development Life Cycle (SDLC)
  - Quality documentation

- Full transparency to community (e.g. the Bazaar)

“Given enough eyeballs, all bugs are shallow.” - E.S. Raymond

“In the open-source software world, bug reports are welcome.” – A. Gelman
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