# Considerations for Assuring Quality Tools and a Proposal for Open Software Development Standards
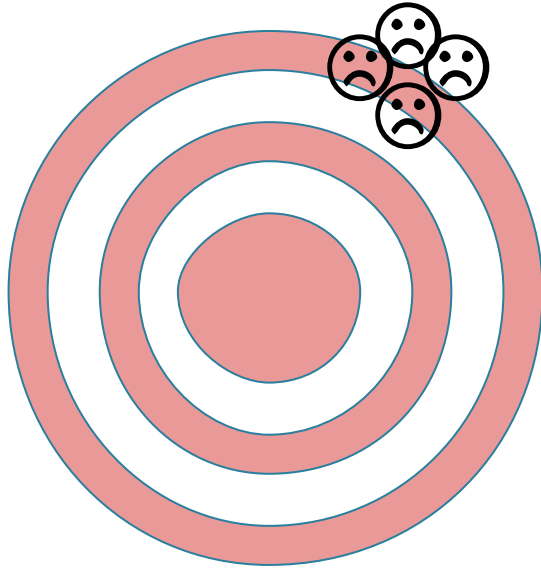
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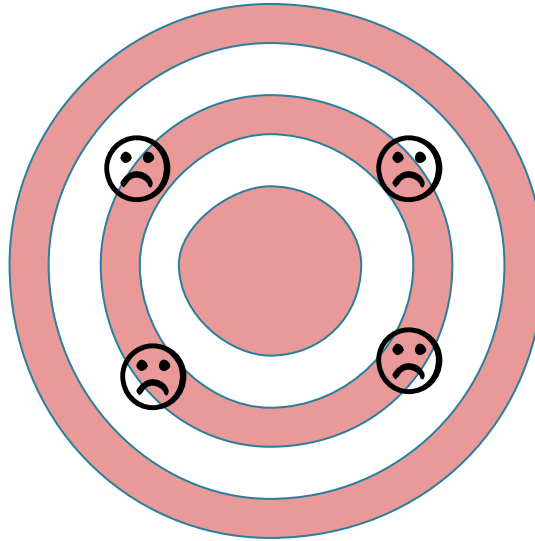
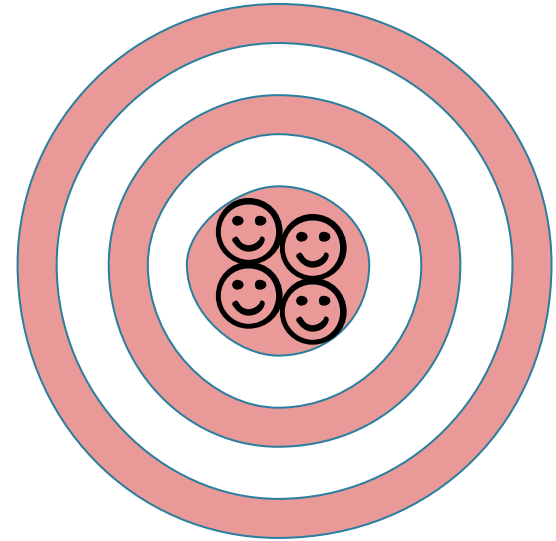# Bedside Pharmacometrics, aka...

**Precision Medicine**

**Accuracy Medicine**

**Personalized Medicine**

# Considerations for Quality Bedside PMX Tools

**Scientific Validity**

**Algorithm Verification**

**Software Development Process**

**Interoperability and Accessibility**

**Scientific Validity**

- 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



136 patients met the inclusion criteria

53 patients were excluded:
- 25 no follow-up or incomplete data
- 11 previously exposed to IFX
- 9 first maintenance infusion <week 14
- 5 planning pregnancy
- 2 no ATI/IFX measurments
- 1 enrolled in another study

83 patients were eligible for the analysis

16 patients
Mono pTDM

32 patients
Mono SOC

35 patients
Combo SOC
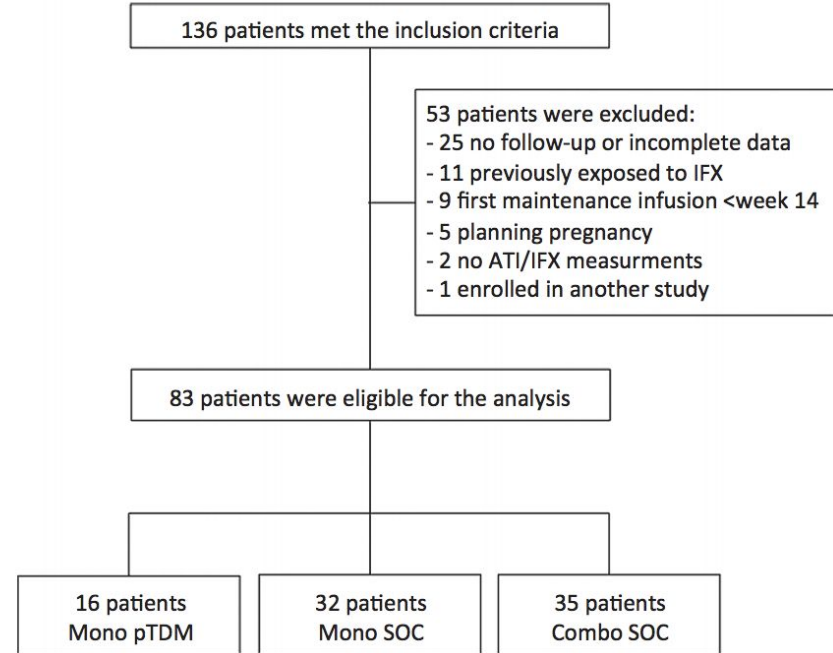
FIGURE 1. Flow chart of patients evaluated for the study and distribution within the study groups.

Lega et al. Inflamm Bowel Dis. 2019 Jan 1;25(1):134-141. doi: 10.1093/ibd/izy203

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."
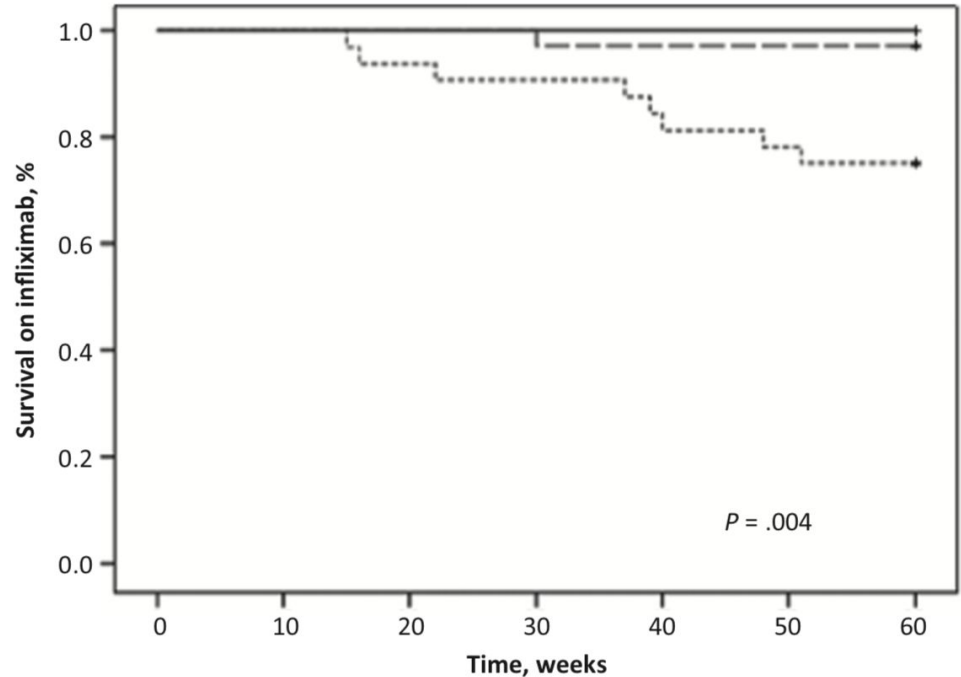
**Algorithm Verification**

- How will model-based methods inform clinical decision-making?

    - Estimation of model parameters

    - Projection of expected concentration or response time-course

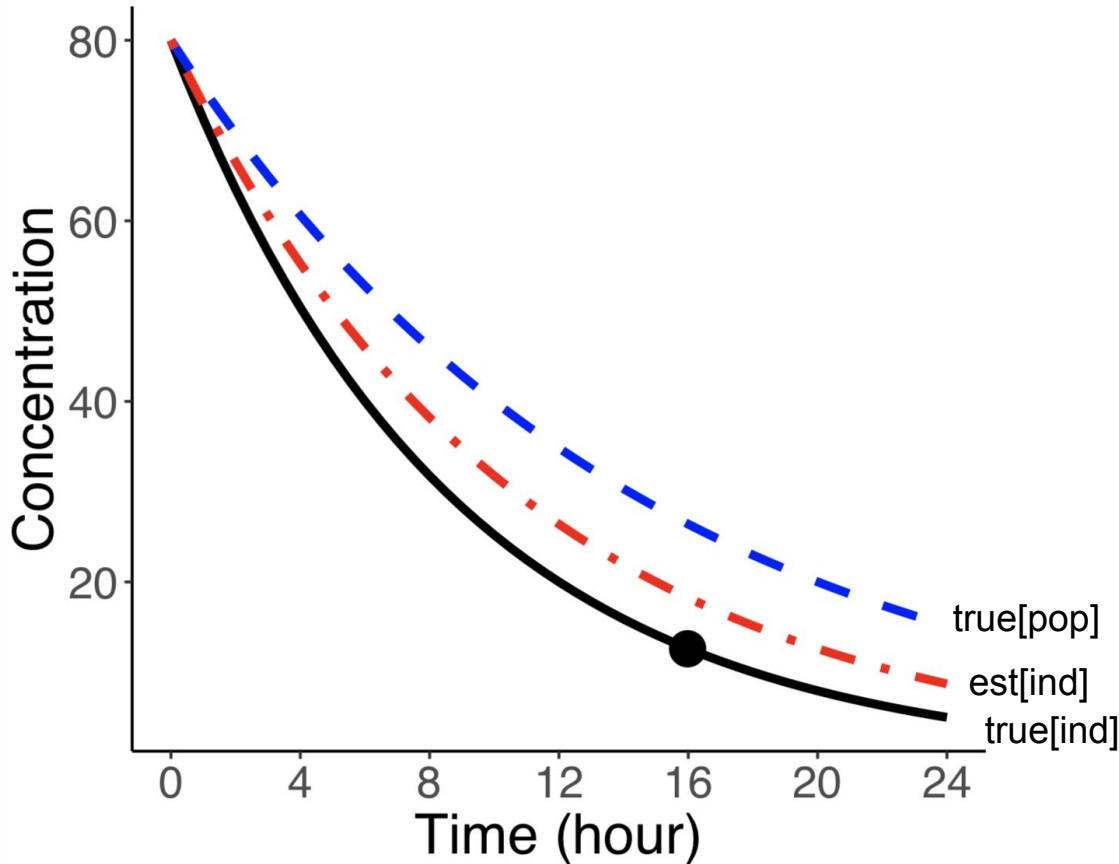- Has the algorithm performance been evaluated under realistic conditions?

# Algorithm Verification: MAP Bayes Estimation
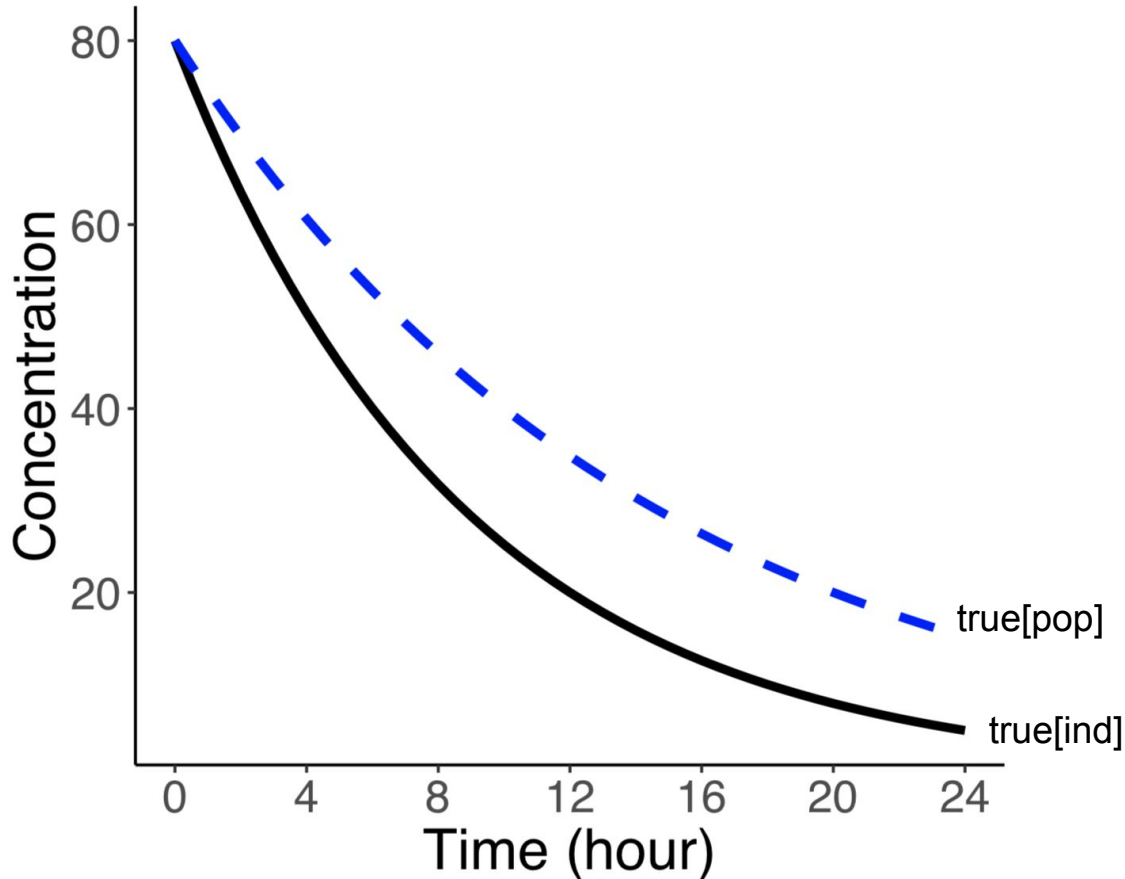


- Which way will the balance tip between prior knowledge and new data?

- Individual estimation is driven by relative magnitude of residual variability vs. inter-subject variability
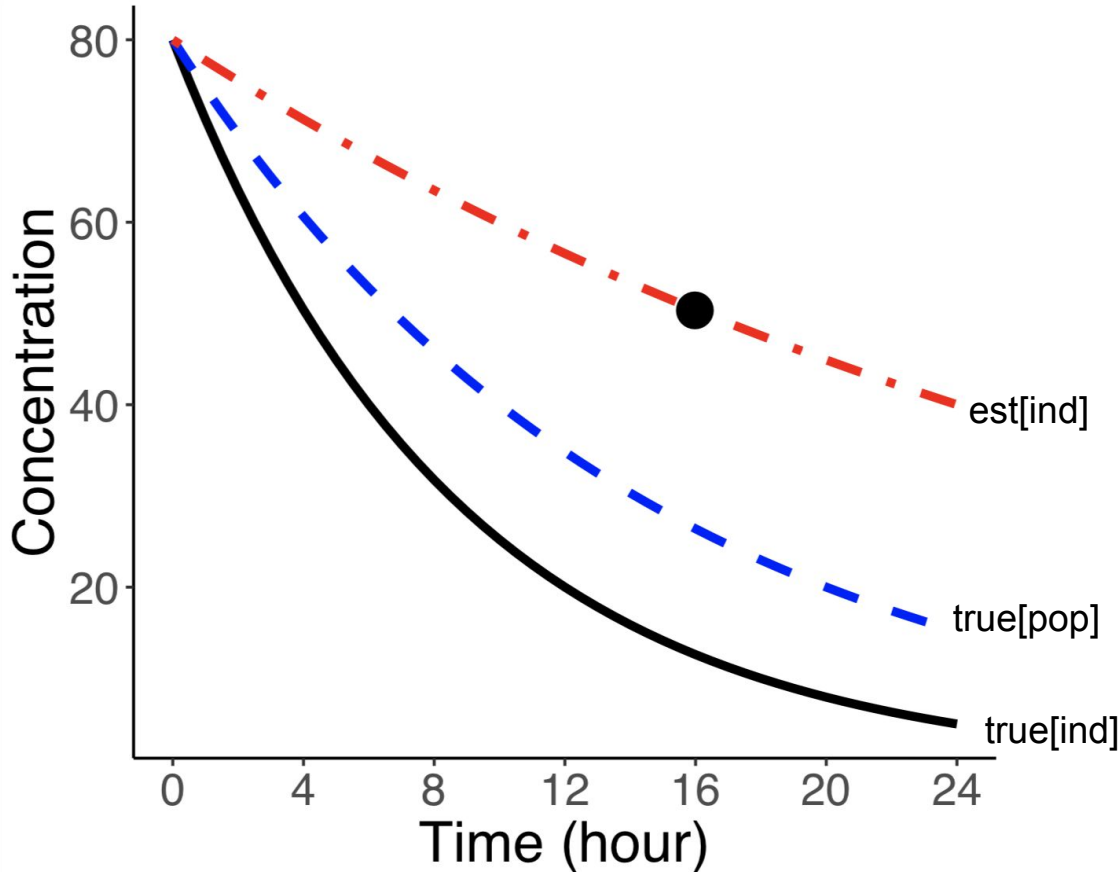
# Algorithm Verification: MAP Bayes Estimation

- 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

**Software Development Process**

- Does software development follow professional and regulatory standards?

  - A formal software development life cycle process

  - Software validation with documentation

# Software Development Life Cycle

Waterfall

Agile

https://www.digite.com/blog/waterfall-to-agile-with-kanban/
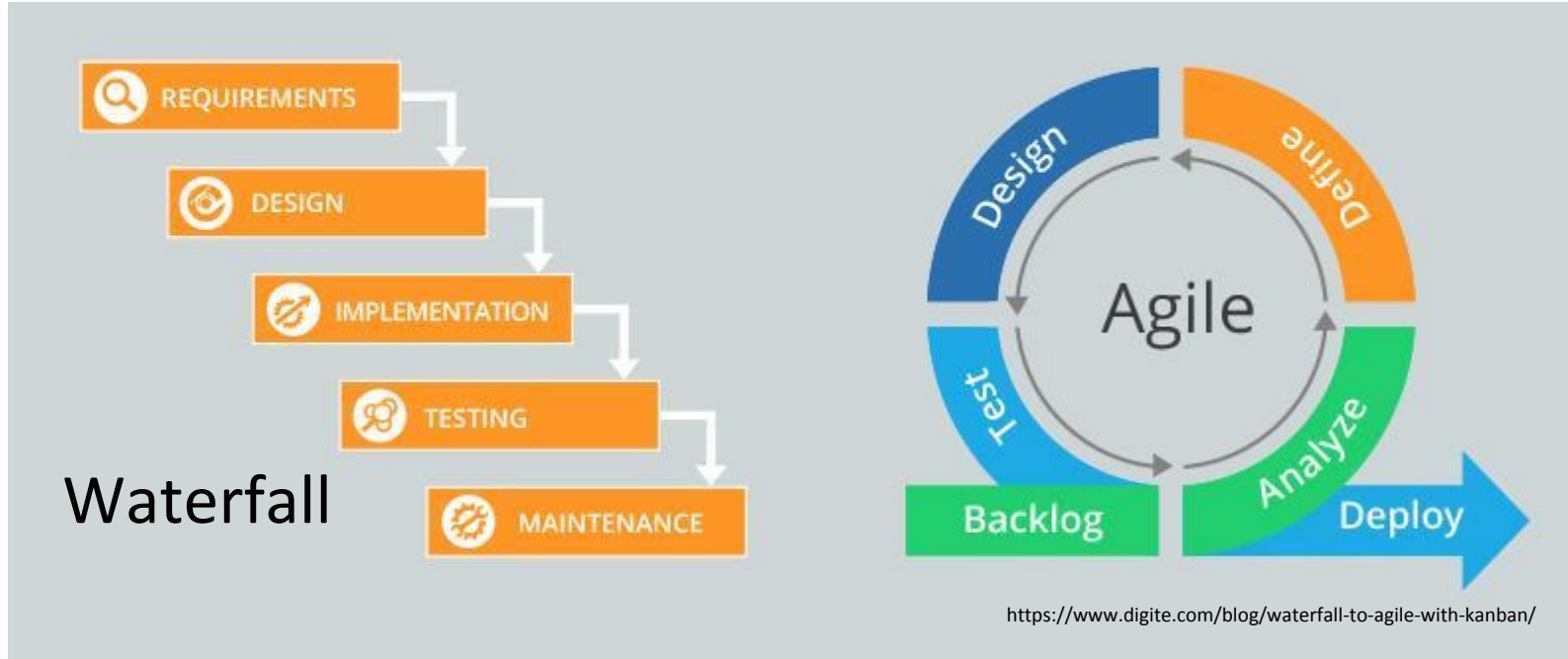
**Open SDLC -** https://github.com/metrumresearchgroup/open-sdlc

**Interoperability and Accessibility**

- 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?

# Open Source Software in Pharmacometrics
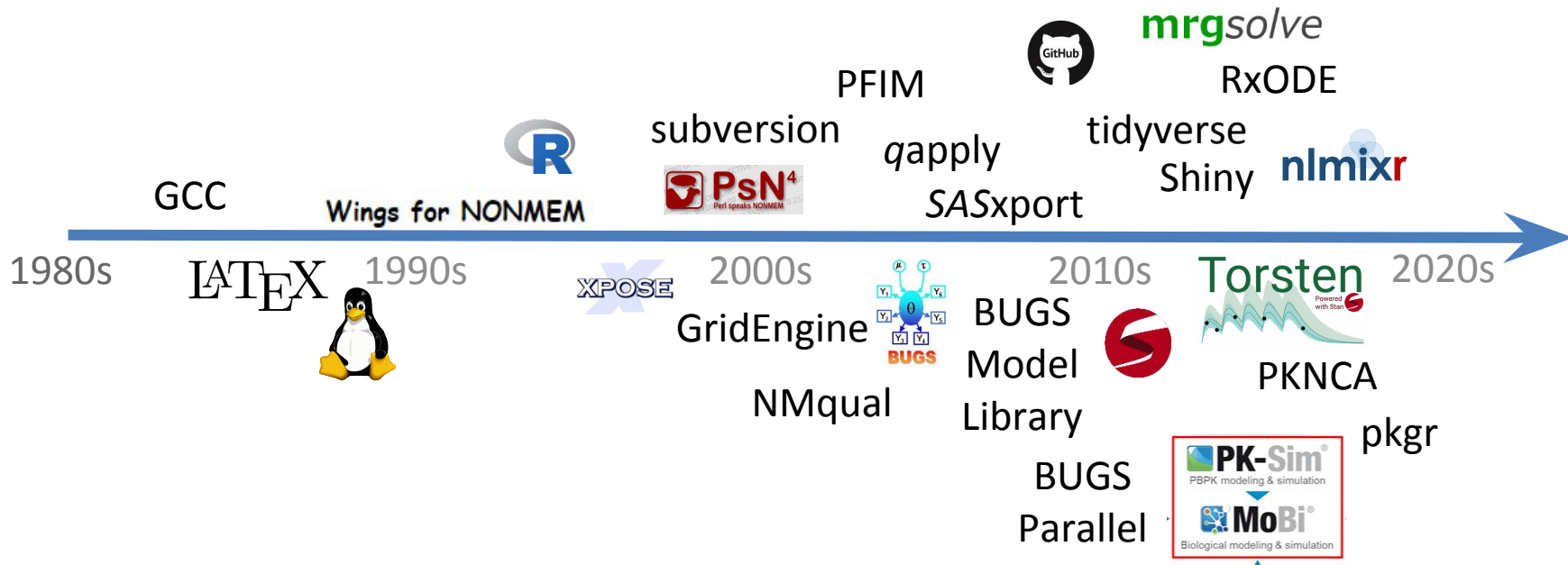
Adapted from: Brian Corrigan, ACoP 2016.
Display may not be inclusive of all open source, public license software used in pharmacometrics.
Suggestions for additions welcome. Send software name, url, and license type to marcg@metrumrg.com.

# 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

# Considerations for Quality Bedside PMX Tools

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# Thank You

Presentation available at https://metrumrg.com/publications/