The evolution of clinical decision support tools that enable precision dosing at the point of care

FDA Precision Dosing Workshop
Sirj Goswami
August 12th, 2019
An ideal CDS platform should be **user friendly, scalable, integrated into the clinical workflow and improve healthcare outcomes**.
HISTORICAL CONTEXT

First model-informed precision dosing (MIPD) tool developed in 1969

PK/PD Models to support clinical decisions

Computers and Biomedical Research
Volume 2, Issue 6, December 1969, Pages 507-518

Computer-aided long-term anticoagulation therapy
Lewis B. Sheiner

Abstract
A computer program is described which calculates a suggested daily anticoagulant dose schedule for a patient. The program requires previous prothrombin times and drug dosages as well as physician determined therapeutic goals and limits. A simple compartmental response model is used to predict prothrombin time responses from previous drug doses. Suitable future dose suggestions are calculated from these prothrombin time predictions. A retrospective study provided a test of the program's performance relative to that of resident physicians and three staff cardiologists at a large teaching hospital. The doses computed by the program were found to compare favorably with those of the pilot sample of physicians.
Current environment: **Fragmented** dosing calculators and spreadsheets that **do not** leverage the power of MIPD

- Imprecise (not-model based)
- Difficult to use
- Fragmented
- Requires manual entry
- Lack of standardization
The **time is right** to adopt CDS Platforms and MIPD in healthcare

**Technical Barriers Eliminated**

- Cloud-based infrastructure for healthcare, computational power
- Transition to Electronic Medical Records
- Rise of diagnostics

**Macro-level Industry Trends**

- Value-based healthcare (pay for value)
- Data-driven patient care
- Precision medicine
CDS Platforms outside of MIPD have undergone a transformation over the past several years.

**Key Evolving Characteristics**
- User interface/experience
- Software integration
- Clinical workflow implementation
- Analytics
User interface (UI) / user experience (UX)
## UI/UX

UI/UX in healthcare lags behind other industries

- Electronic health record (EHR) systems are outdated
- Complex clinical workflows
- Multiple stakeholders involved in decision making
- Waterfall software design process
- Clinical user is NOT the buyer
- Developers are NOT users and NOT in tuned with clinical need
- Complexity of data inputs and data outputs
- Abundance of idiosyncratic terminologies (e.g. AUC)
What constitutes an optimal user experience?

The product is **useful**
- It addresses real pain points and problems for the user population.

The product is **user friendly**
- Users can intuitively, or with relatively little training, repeatedly use the product’s functionality.

The product is **simple**
- Users demand a simple platform that does not compromise quality.

**Know-how**
- Expert
  - Domain expert
  - Clinical pharmacologist
  - Specialized pharmacists

**Empathy**
- Typical user
  - Not a domain expert
  - Physician
  - Pharmacist

**Product**
-
Usability research studies help us achieve an optimal product design.

Develop initial prototype
- Incorporate “expert” user perspective
- Make concept real

Conduct qualitative research
- Assess user behavior
- User acceptance surveys
- Uncover actual, real pain points

Translate insights into product design
- Develop mockups and frameworks
- Merge observations with heuristics

Validate and continuously improve product design
- Update actual CDS UI/UX
- Iterate on usability with user-feedback
Updated User Interface Resulting From Usability Studies
UI/UX
Consolidated Dashboard Improves Workflow Efficiency

Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Serum creatinine</td>
<td>0.8 mg/dL</td>
</tr>
<tr>
<td>Weight</td>
<td>57 kg</td>
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<tr>
<td>Height</td>
<td>168 cm</td>
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<tr>
<td>Creatinine assay</td>
<td>Enzymatic</td>
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<tr>
<td>eGFR estimation</td>
<td>Cockcroft-Gault</td>
</tr>
<tr>
<td>Absolute eGFR</td>
<td>56.7 ml/min</td>
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<tr>
<td>Relative eGFR</td>
<td>59.7 ml/min/m²</td>
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<tr>
<td>Weight for eGFR</td>
<td>Total body weight</td>
</tr>
<tr>
<td>Adjusted weight</td>
<td>53.8 kg</td>
</tr>
<tr>
<td>Ideal weight</td>
<td>59.6 kg</td>
</tr>
<tr>
<td>BSA</td>
<td>1.64 m²</td>
</tr>
<tr>
<td>BMI</td>
<td>20.2 kg/m²</td>
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<tr>
<td>Fat-free mass</td>
<td>38.5 kg</td>
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</table>

Dose information

<table>
<thead>
<tr>
<th>Interval</th>
<th>Start time</th>
<th>Infusion length</th>
<th>TDM</th>
<th>Since dose</th>
<th>Comments</th>
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PK curve

How does this change the PK curve?

Fit info

How does this show up on the fit info?

Cover the measured vs expected

No flag, so maybe just hedge a little bit
UI/UX
Consolidated Dashboard Improves Workflow Efficiency

Dosing Reference Table

Reference table

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Dose (mg)</th>
<th>Interval</th>
<th>AUC</th>
<th>Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>-56.7%</td>
<td>250 mg</td>
<td>12 hours</td>
<td>1 hour</td>
<td>250 μg/L/hr</td>
</tr>
<tr>
<td>-33.3%</td>
<td>500 mg</td>
<td>12 hours</td>
<td>1 hour</td>
<td>497 μg/L/hr</td>
</tr>
<tr>
<td>previous</td>
<td>750 mg</td>
<td>12 hours</td>
<td>1 hour</td>
<td>743 μg/L/hr</td>
</tr>
<tr>
<td>-33.3%</td>
<td>1000 mg</td>
<td>12 hours</td>
<td>1 hour</td>
<td>980 μg/L/hr</td>
</tr>
<tr>
<td>-56.7%</td>
<td>1250 mg</td>
<td>12 hours</td>
<td>1.5 hours</td>
<td>1235 μg/L/hr</td>
</tr>
</tbody>
</table>

Footnote: *PAUC probability that AUC is >400 (efficacy); PUC: probability that C_{peak} is above 20 μg/mL (tolerability); T: Probability of nephrotoxicity, based on Lodise et al. Clin Infect Dis 2009.
UI/UX
Consolidated Dashboard Improves Workflow Efficiency
Integration into the clinical workflow
EHR INTEGRATION

Why is it so challenging?

- EHR systems are very closed off (Not interoperable)
- Many different standards and architectures for exchange
- Many different implementations of data interchange
- EHR integration requires scarce IT resources
- Clinical workflow within EHR is unclear
## EHR Integration

Different methodologies to overcome integration challenges

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
<th>Pros</th>
<th>Cons</th>
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| Custom Integration            | Custom integration involves the consideration and agreement between integration partners of the methods of integration (technology stack, security methods, onsite/VPN vs internet, batch processing vs real-time, embedded vs standalone, etc.) | • Control over integration approach  
• Can potentially allow integrations when there are no other options | • IT staff needs to be highly skilled at custom integration work and have capacity  
• IT time/effort  
• Not scalable/reusable  
• Minimal support |
| HL7                           | HL7 integration involves setting up import/export data endpoints for the transmission of standardized HL7 messages but with the generation of a mapping/transform layer to handle customizations. | • International messaging standard for clinical data  
• Widely adopted (as of 2018) | • Extensive customization resulting in extra integration work  
• IT time/effort  
• Message semantics not necessarily consistent |
| EMR Vendor APIs (e.g. Epic, AllScripts, Cerner, Athena Health) | EMR vendors provide their own access methods to their data. External parties must get approval from both the vendor and institutions that use their systems as well as implement vendor-specific data access solutions through the APIs that the vendors provide. | • EMR vendor responsible for data access and support  
• Web-based APIs available | • Each vendor has their own set of APIs  
• Technologies may be complex and difficult to use  
• Data access methods may be mixed (e.g. APIs + HL7) |
| EHR Vendor App Stores         | EHR vendors also provide solutions modeled after the Apple App Store or Google Play distribution service where 3rd parties can develop their applications (under the vendor’s protocol for app store development) and make them available for distribution through the store. | • Use of standardized, modern REST APIs in most cases (FHIR)  
• Scalable / easier application distribution  
• Simplified integration setup | • Cost of integration with EHR vendor |
| Third Party Applications      | If a clinical application/data provider has a FHIR server that is made accessible to 3rd parties seeking data, these 3rd parties can develop FHIR API clients which have the ability to access this data using a modern, standards-based, REST API. | • Standards-based APIs and protocol  
• Modern REST-based APIs and authentication schemes  
• Granular access to clinical data  
• Ability to easily integrate applications into EMRs via HTML5 | • 3rd parties may not have full implementations of FHIR resources  
• FHIR specification evolves at a faster pace than adoption (version issues) |
### EHR INTEGRATION

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*Most scalable*
Integration through a EHR app store
Third Party Applications: Integration through open standards using FHIR

Clinical surveillance system (Theradoc)

CDS Tool
Clinical Analytics
# Why is data collection post-implementation necessary?

## Key Questions Post-Implementation

### Institution-specific
- What is the clinical benefit to using the tool?
- Will we save money by improving patient outcomes?
- Are users satisfied with the product? Is it being used?
- What is the operational benefit to my organization?
- Will the module work in other indications? Other patient populations?

### Beyond the institution
- How do we improve implementation process at other institutions?
- How can we collect the right data to demonstrate clinical value and identify the right predictors of drug response?

## Key Hospital Stakeholders

<p>| | |</p>
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<tbody>
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<td>Chief Medical Officer</td>
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<tr>
<td>Director of Pharmacy</td>
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<tr>
<td>Chief Quality Officer</td>
<td></td>
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<tr>
<td>Clinical Pharmacist</td>
<td></td>
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<tr>
<td>Physician</td>
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</table>
A well architected framework will enable the proper collection of data to address post-implementation questions.

**Clinical Analytics and Continuous Learning**
- Machine learning capabilities
- Derive clinical/operational metrics
- Link PK/PD to outcomes
- Show cost benefit at hospital

**Administrator/Key Stakeholder**
- What is the clinical benefit to using the tool?
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- Will the module work in other indications? Other patient populations?
Framework enables a real-time assessment of clinical and operational data
Future of Precision Dosing
Precision dosing by leveraging **patient** and **population** level learning.

**Data Flow**

- **Patient Level Learning**
  - Model-informed precision dosing
  - Bayesian forecasting

- **Population Level Learning**
  - Machine learning
  - Optimize treatment guidelines and models

**Updated Models / Treatment Protocols**
Thank you

Further Reading:


3. Goswami, S., Overcoming Adoption Barriers of Cloud-Based Precision Dosing. ASCPT Webinar (2018)

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