Application of Virtual Clinical Trials in Dialysis Patient Care

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Peter Kotanko, MD FASN
Renal Research Institute
New York, NY
Disclosures

• I am an employee of the Renal Research Institute, New York, NY, a wholly owned subsidiary of Fresenius Medical Care (FMC)

• I hold stock in FMC

• I receive author royalties from UpToDate
Randomized controlled trials (RCTs)

- RCTs are assigned the highest level of evidence for therapeutic studies.
- A well-designed and properly conducted RCT will give unbiased results and have little risk of systematic errors (i.e., have a high **internal validity**).
- RCTs may face weaknesses that limit their generalizability, because RCT participants may not be representative of the wider population of interest (i.e., have poor **external validity**).
- In addition, RCT results must also generalize to the real-life settings in which the trial results will later be applied (i.e., should have a high **ecological validity**).
- Other frequently noted shortcomings are the need to recruit a sufficiently large number of patients, high costs, the need to establish a sophisticated trial infrastructure, and the long duration from study inception to completion.
Randomized controlled trials are assigned the highest level of evidence for therapeutic studies.
RCT - challenges

• With multiple treatments in the pipeline, pharmaceutical companies and academic institutions compete for a limited pool of patients.

• In oncology, it has been estimated that only 20% of patients are eligible for clinical trials, because many patients are excluded due to poor performance status or inability to meet specific eligibility requirements (Wujcik, *J Health Care Poor Underserved*, 2010).

• This limitation has been illustrated by a study showing that filling all pancreatic-cancer trials in the United States in 2011 would have required the participation of 83% of patients with resectable pancreatic ductal adenocarcinoma, yet, only 5% of patients volunteer for trials (Hoos, *J Clin Oncol*, 2013).

• Other areas of medicine face comparable challenges.
Difficulties of trial enrollment (Sergeyeva, J Nephrol, 2012)

For the Frequent Hemodialysis Network (FHN) Trial

- We screened 6,276 hemodialysis (100%)

- 3,481 (55%) were considered eligible

- 3,124 (50%) were approached for consent

- 378 (6%) consented,

- 245 (4%) were randomized
Is there a way to expand the classical clinical trial framework?

This is almost like asking “Is there an alternative to using living humans for car-safety test?”

What are we doing in current car-safety testing?
Crash test dummies instead of living humans

Crash test dummy design

• Requires comprehensive quantitative understanding of biomechanics
• **Physical** representation of the essential components of human biomechanics in dummies
• Crash test dummies are subjected to multiple test
• Results are extrapolated to human beings
These are the required steps

Crash test dummies in car design

- Understand in-depth the biological and mechanical aspects relevant to the problem, such as height, weight, age, body composition, mass distribution, joint and bone biomechanics, etc.
- Neglect irrelevant aspects, such as skin color, eGFR, IQ, erythropoiesis, etc.
- Build dummies representative of the car-driving population
- Subject these dummies to experiments
- Learn from these experiments and draw generalizable conclusions
- Innovation roll-out
- Observe real-world results
- Refine crash test dummies if necessary

“Crash test dummies” (we call them Avatars) in medical applications – anemia example

- Understand in-depth the biological basis relevant to the problem, such as bone marrow biology, drug pharmacokinetic and –dynamic, etc.
- Neglect irrelevant aspects
- Build a generic mathematical model representing the biology of interest
- Create individual avatars (=mathematical representations of real patients) by parameter identification
- Subject these avatars to experiments (virtual trial) and draw generalizable conclusions
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Crash test dummy vs. Trial Avatar

Crash test dummy

- Requires comprehensive quantitative understanding of biomechanics
- **Physical** representation of the essential components of human biomechanics in dummies
- Crash test dummies are subjected to multiple test

Avatar (example anemia therapy)

- Requires comprehensive quantitative understanding of erythropoiesis
- **Mathematical** representation of the essential aspects of erythropoiesis in Avatars
- Avatars are subjected to multiple anemia treatment schemes
Ingredients that are key to success

Success = Mathematics
These are the required steps

Crash test dummies (we call them Avatars) in medical applications – anemia example

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Exemplified in the context of anemia dosing and administration strategies in hemodialysis (HD) patients.

- HD patients suffer from a severe impairment or failure of the kidneys
- HD patients undergo dialysis 3x/week for 3-4 hours in a clinic.
- Anemia is a decrease in red blood cells (RBC) or hemoglobin
- Almost all patients suffering from ESRD develop anemia at some point
- Renal anemia is
  - often severe,
  - difficult to treat,
  - wide variation in response to therapy

## Healthy subject vs. ESRD patient

<table>
<thead>
<tr>
<th>Biological variable</th>
<th>Healthy subject</th>
<th>ESRD patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites of EPO production</td>
<td>Kidneys and liver</td>
<td>Liver with variable (if any) renal contribution</td>
</tr>
<tr>
<td>Regulation of EPO concentration</td>
<td>Fine-tuned feedback loops</td>
<td>Man-made EPO algorithms</td>
</tr>
<tr>
<td>Bone marrow EPO responsiveness</td>
<td>Normal</td>
<td>Variable from almost normal to severely impaired</td>
</tr>
<tr>
<td>RBC life span (days)</td>
<td>120 – 140</td>
<td>Variable between 30 – 120 (mean ~70)</td>
</tr>
<tr>
<td>EPO half live (hours)</td>
<td>~ 5</td>
<td>Variable 4 – 14</td>
</tr>
<tr>
<td>Neocytolysis (&quot;suicidal RBC death&quot;)</td>
<td>Minimal</td>
<td>Variable from minimal to severe</td>
</tr>
<tr>
<td>Fluid status</td>
<td>Stays within narrow limits</td>
<td>Variable over a wide range</td>
</tr>
<tr>
<td>Iron availability</td>
<td>Sufficient</td>
<td>Variable from almost normal to severely impaired</td>
</tr>
</tbody>
</table>
A Powerhouse Named Bone Marrow: Development of Red Blood Cells

- **Bone Marrow**
- **Reticulocytes & Red Blood Cells**
- **Progenitor Cells**
  - "BFU-E"
  - "CFU-E"
- **Precursor Cells**
  - Orthohematopoietic erythroblasts
  - Basophilic erythroblasts
  - Polychromatophilic erythroblasts
Mathematical Modeling of Reproduction of RBCs

“A model of erythropoiesis in adults with sufficient iron availability”

— STAN GUDDER
Formulate the Mathematical Model

Cell proliferation, maturation velocity, and apoptosis of erythroid cells are influenced by erythropoietin (EPO).

| BFU-E | $\frac{\partial}{\partial t}p(t,x^p) + \frac{\partial}{\partial x^p}p(t,x^p) = \beta^p p(t,x^p)$, |
| CFU-E | $\frac{\partial}{\partial t}q(t,x^q) + \frac{\partial}{\partial x^q}q(t,x^q) = (\beta^q - \alpha^q(E(t)))q(t,x^q)$, |
| Erythoblasts | $\frac{\partial}{\partial t}r(t,x^r) + \frac{\partial}{\partial x^r}r(t,x^r) = \beta^r r(t,x^r)$, |
| BM Reticulocytes | $\frac{\partial}{\partial t}s(t,x^s) + \nu^+(E(t)) \frac{\partial}{\partial x^s}s(t,x^s) = -\alpha^s s(t,x^s)$, |
| Erythrocytes | $\frac{\partial}{\partial t}m(t,x^m) + \frac{\partial}{\partial x^m}m(t,x^m) = -\alpha^m(E(t),x^m)m(t,x^m)$, |
| endogenous Epo | $\frac{d}{dt}E^{\text{end}}(t) = \frac{1}{TBV}E_{\text{in}}^{\text{end}}(t) - c_{\text{deg}}^{\text{end}}E^{\text{end}}(t)$, |
| exogenous Epo | $\frac{d}{dt}E^{\text{ex}}(t) = \frac{1}{TBV}E_{\text{in}}^{\text{ex}}(t) - c_{\text{deg}}^{\text{ex}}E^{\text{ex}}(t)$, |
Model Validation – Example Blood Donation

Data from Pottgiesser et al, Transfusion 2008
These are the required steps

Crash test dummies (we call them Avatars) in medical applications – anemia example

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Model Adaptation to Individual Patients using Parameter Estimation: Avatar Generation

- Model has 30 parameters
- 2 parameters are adjusted using empirical formulas
  - Data: gender, height, weight
- 5 parameters are inferred from data
  - Data: hemoglobin levels, ESA administration; anthropometric data
- Minimize a weighted least square cost functional
  \[ J(p_1, \ldots, p_n) = \sum_{j=1}^{N} w(t_j) (y(t_j) - \phi(\theta, t_j))^2 \]
- Model was adapted to 60 ESRD patients
What is the process?

Input:
- Hemoglobin
- ESA use
- Anthropometric data

Parameter identification

Output:
- RBC life span, EPO half life, bone marrow response to EPO (2 parameters), endogenous EPO production
Comparison of model simulations and empirical data

Pre-dialysis Hgb measurements (magenta) and model output (blue) during the model adaptation period (yellow area) and prediction period (purple area). Green bars represent the administered ESA doses.

Fuertinger (2018)
Comparison of model simulations and empirical data

Pre-dialysis Hgb measurements (magenta) and model output (blue) during the model adaptation period (yellow area) and prediction period (purple area). Green bars represent the administered ESA doses.

Fuertinger (2018)
Prediction of hemoglobin values in Virtual Dialysis Clinic Avatars

Fuertinger (2018)
Prediction of RBC life span in Virtual Dialysis Clinic Avatars

Fuertinger (2018)
What to do now with these Avatars?

• We created thousands of anemia Avatars that are an un-biased representation of the 160K+ FMCNA hemodialysis patients

• These Avatars are the pulled together and “live” in what we call a Virtual Dialysis Clinic (VDC)

• The VDC grows steadily and is developed as the “dialysis ecosystem” evolves over time

• The VDC is the core of our Virtual Trials (VTs)
These are the required steps

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<table>
<thead>
<tr>
<th></th>
<th>Avatars</th>
<th>reference population</th>
<th>random group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>6,659</td>
<td>79,426</td>
<td>6,659</td>
</tr>
<tr>
<td>Male (%)</td>
<td>54%</td>
<td>55%</td>
<td>55%</td>
</tr>
<tr>
<td>Race (White)</td>
<td>57%</td>
<td>61%</td>
<td>60%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.1 ±13.9</td>
<td>65.6±14</td>
<td>65.9±14.1</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>29.4 ±7.6</td>
<td>29.1±7.5</td>
<td>29 ±7.5</td>
</tr>
<tr>
<td>Vintage (years)</td>
<td>3.4 (1.7, 5.8)</td>
<td>2.3 (0.7, 5)</td>
<td>2.3 (0.7, 4.9)</td>
</tr>
<tr>
<td>Comorbid diabetes (%)</td>
<td>64%</td>
<td>64.50%</td>
<td>65%</td>
</tr>
<tr>
<td>Hemoglobin (mg/dL)</td>
<td>10.6 ±0.5</td>
<td>10.7±0.7</td>
<td>10.7±0.7</td>
</tr>
<tr>
<td>Pre-treatment weight (kg)</td>
<td>81.8 (68.6, 98.1)</td>
<td>81.4 (68.1, 98)</td>
<td>81.3 (68, 98)</td>
</tr>
<tr>
<td>Pre-treatment SBP (mmHg)</td>
<td>150.1 ±17.6</td>
<td>148.5±18.4</td>
<td>148.5±18.5</td>
</tr>
<tr>
<td>Post-treatment SBP (mmHg)</td>
<td>138.2 ±16</td>
<td>137.9±16.4</td>
<td>138.1±16.6</td>
</tr>
<tr>
<td>Treatment time (min)</td>
<td>221.3 ±25.4</td>
<td>222.7±28.6</td>
<td>222.3±27.3</td>
</tr>
<tr>
<td>Ultrafiltration volume (kg)</td>
<td>2.44 ±0.93</td>
<td>2.3±0.9</td>
<td>2.33±0.9</td>
</tr>
<tr>
<td>Interdialytic weight gain (%)</td>
<td>3 (2.3, 3.6)</td>
<td>2.9 (2.3, 3.5)</td>
<td>2.8 (2.2, 3.5)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.9 ±0.32</td>
<td>3.8±0.4</td>
<td>3.8±0.4</td>
</tr>
<tr>
<td>Iron dose (mcg/month)</td>
<td>250 (150, 500)</td>
<td>250 (150, 500)</td>
<td>250 (150, 500)</td>
</tr>
<tr>
<td>Dialysate sodium (mEq/L)</td>
<td>137 (137, 138)</td>
<td>137 (137, 138)</td>
<td>137 (137, 138)</td>
</tr>
<tr>
<td>Neutrophils to lymphocytes ratio</td>
<td>3.6 (2.7, 5)</td>
<td>3.7 (2.7, 5.2)</td>
<td>3.7 (2.7, 5.2)</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>34±8.1</td>
<td>33.6±8.9</td>
<td>33.7±9</td>
</tr>
</tbody>
</table>
How well do simulation done in the Virtual Clinic resemble reality?

• **Virtual Anemia Trial 1.0**: Using virtual patients created by Monte Carlo sampling. A cohort of 6,659 virtual patients was created by randomly sampling unique parameter values from a parameter space defined a priori.

• **Virtual Anemia Trial 2.0**: Using personalized avatars to improve external validity. A virtual patient population of 6,659 avatars was created using routinely collected clinical data from individual patients undergoing HD treated for anemia.

• **Virtual Anemia Trial 3.0**: We added stochastic modules resembling the HD ecosystem to improve ecological validity. The avatar population was subjected to the identical anemia treatment protocol as in trials 1.0 and 2.0. However, we incorporated clinic modules in the simulations to increase ecological validity.
Results Virtual Anemia Trial 1.0

(a) Distribution of hemoglobin values

(b) Frequency of ESA dose administration

The Virtual Anemia Trial: An Assessment of Model-Based 
*In Silico* Clinical Trials of Anemia Treatment Algorithms 
in Patients With Hemodialysis

Doris H. Fuhringer, Alice Topping, Franz Koppel, Stephan Thijssen and Peter Koterko
Results Virtual Anemia Trial 2.0
Setup schematic of Virtual Anemia Trial 3.0.

Blue boxes: “deterministic” modules

Green boxes: “stochastic” modules, simulating the (random) impact of the laboratory (e.g., measurement noise), physician (e.g., blood transfusion orderings), dialysis facility (e.g., nonadherence of patients to therapy), and hospital (e.g., hospital stays).
Results Virtual Anemia Trial 3.0

(e) Distribution of hemoglobin values

(f) Frequency of ESA dose administration
Additional trial comparisons

Virtual Anemia Trial 2.0

Virtual Anemia Trial 3.0
# Reality check - Model Parameters

<table>
<thead>
<tr>
<th></th>
<th>Model (N = 6130)</th>
<th>Study/Literature Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RBC Lifespan [days]</strong></td>
<td>75 ± 20 (33,136)</td>
<td>74 ± 23 (30,125)</td>
</tr>
<tr>
<td><strong>Endogenous erythropoietin [U/l]</strong></td>
<td>16.4 ± 8.4 Tertiles: 11.08 , 18.17</td>
<td>9.1 ± 4.5* Tertiles: 10.6 , 16.0**</td>
</tr>
<tr>
<td><strong>Mircera® half-life [hours]</strong></td>
<td>127 ± 53</td>
<td>134 ± 64</td>
</tr>
<tr>
<td><strong>Apoptosis of CFU-Es</strong></td>
<td>Median: 0.008 (0.0015,0.021)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Maturation velocity of reticulocytes</strong></td>
<td>Median: 0.0333 (0.0029,0.1841)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

RBC Lifespan: RRI Study; 45 patients (Ma, et al., 2017)
Endogenous Epo: *Ifudu et al, Nephron 1998; 20 hemodialysis patients (all receiving recombinant erythropoietin)
**Wagner et al, CJASN 2011; 215 Diabetic CKD patients
Mircera half-life: FDA label
What have we learned so far?

• Creation of mathematical models (usually systems of ODEs and PDEs) of physiological systems is feasible (this has been known since decades)
• Parameter identification allows us to create Avatars and to gain patient-specific medical insights (this has been known, but was not applied on a large scale)
• Large Avatar populations can be submitted to Virtual Trials (this is novel)
• The results of Virtual Trials can be substantially improved by including deterministic or stochastic modules that reflect the health care ecosystem (this is novel)
Ecosystem in the automotive field
Practical Applications
ESA prescription process in our clinics

Data: Hgb; previous ESA dose → Central Computer-based Anemia Algorithm → New ESA dose recommendation → OK
ESA prescription process in our clinics

Data: Hgb; previous ESA dose

NEW Central Computer-based Anemia Algorithm

New ESA dose recommendation

✅
These are the required steps

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Pre / Post Evaluation of a Treatment Algorithm Developed in Virtual Trials

The best treatment algorithm has been **used in >1,000 dialysis clinics for treating > 100,000 patients:**

- More patients in hemoglobin target
- Lower EPO utilization
- Lower therapy costs

Development of average EPO doses after clinics switched to the anemia algorithm tested in the Virtual Dialysis Clinic.

2013
Roll-out of the first anemia protocol developed and tested in the Virtual Clinic
Ongoing Cluster-Randomized Evaluation of a Treatment Algorithm Developed in Virtual Trials

**ELIGIBLE CLINICS**  
(N=438)

**CASES:**  
V 4.0 Algorithm  
(N=219)

**RANDOMIZATION**

**CONTROLS:**  
V 3.0 Algorithm  
(N=219)

**More** patients in target  
(Hgb 10-11 g/dL)

**Less** patients with Hgb below 9 g/dL

**Less** Mircera® utilization
Can the Virtual Clinic / Virtual Trial concept be extended beyond anemia?
Application in CKD-MBD

• Bone Mineral Metabolism (BMM) is severely disturbed in ESRD patients
• Bones are among the first organ systems to be impacted by the reduced excretion of solutes such as phosphorus
• A decline in kidney function results in low calcitriol levels and a lowered calcium absorption
• The parathyroid gland produces high levels of parathyroid hormone (PTH) to counteract high phosphate and low calcitriol and calcium levels
• ESRD patients frequently develop parathyroid gland hyperplasia
The Virtual Cinacalcet Trial

• We wanted to explore a potential 3x/week administration of Cinacalcet (off-label use) in dialysis patients treated for elevated PTH levels

• Conducting a clinical study would have taken several years in a large number of patients, and would have been expensive

• A Virtual Cinacalcet Trial was conducted to compare 3x/week with daily administration of Cinacalcet
A Mathematical Model of Parathyroid Gland Biology

\[ \text{Ca} \rightarrow \text{CaSR} \rightarrow \text{VDR} \rightarrow \text{P} \]

- Secretory active cells
- Secretory quiescent cells
- Apoptosis
- Proliferation

Graph: Relative Ca\(^{++}\) concentration over time [days]
Schappacher-Tilp (2019)

Multi-Compartment Model of Cinacalcet Pharmacokinetics
Combining PTH and Cinacalcet Models
Thrice Weekly Cinacalcet Instead of “Daily” – Observations in 4865 HD Patients

<table>
<thead>
<tr>
<th>Ranges [mg/dl]</th>
<th>Phosphate</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3.0</td>
<td>&lt; 8.5</td>
</tr>
<tr>
<td>pre [%]</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>post [%]</td>
<td>48</td>
<td>81</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>3.0-5.5</th>
<th>8.5 – 10.0</th>
<th>&gt; 10.0</th>
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</thead>
<tbody>
<tr>
<td>pre [%]</td>
<td>48</td>
<td>81</td>
<td>5</td>
</tr>
<tr>
<td>post [%]</td>
<td>51</td>
<td>83</td>
<td>4</td>
</tr>
</tbody>
</table>
How do Virtual Trials fit into the current clinical trial framework?
Basic outline of virtual [in silico] trials

**Target population**

**Random sample**

**Virtual trials**
Patients are represented as mathematical constructs ("Avatars")

**Cons:**
- Novelty
- No off-the-shelf solutions
- Time required to develop Avatars
- Only a model of reality, clinical validation required

**Pros:**
- Time: days to weeks once Avatars are created
- Costs: orders of magnitude lower
- No safety concerns
- Generalizability improved
- Multiple trials per Avatar

**Intervention**
- Intervention 1
- Intervention 2
- Intervention 3

**Result**
- Result 1
- Result 2
- Result 3
Can virtual trials complement traditional trial pathways?

Phase 1
Testing for safety and side effects in a small number of volunteers

Phase 2
Testing for safety and effectiveness in a small number of volunteers

Virtual [in silico] trial phase
Extensive high-throughput testing for safety and effectiveness employing computer simulations in appropriate physiologic models of existing patients

Phase 3
Testing for effectiveness, monitoring of side effects, and comparison with other treatments in a large number of volunteers. The testing protocol is informed by the outcome of preceding phases
Summary

• Virtual trials have proven to be fast and highly cost-efficient in testing hypothesis and optimizing treatment algorithms
• Development of physiology-based models require a very close collaboration of multiple disciplines, such as physicians, biologists, data scientists, and mathematicians
Thank you!

Contact: peter.kotanko@rriny.com